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GUIDANCE MODULES ON ANTIRETROVIRAL TREATMENTS

World Health Organization
UNAIDS

Module 1. Introduction to Antiretroviral Treatments

Module 2. Introducing Antiretroviral Treatments Into Health Systems: Economic Considerations

Module 3. ARV Treatments: Planning and Integration Into Health Services

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Module 9. Ethical and Societal Issues Relating to Antiretroviral Treatments

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Guidance Modules on Antiretroviral Treatments

Module 1
Introduction to Antiretroviral Treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)

World Health Organization (WHO)

WHO/ASD/98.1
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Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for preparing the text of this module.

Module 1
Introduction to Antiretroviral Treatments

HIV/AIDS and ARVs in developing countries: the reality

John *found out he was HIV positive in 1989 when he was offered a place at university in the USA. A requirement before taking up his place was a medical examination which included an HIV test. He was devastated when the positive result came back as he not only lost the opportunity of studying abroad but he also had to face the knowledge that he had a terminal illness with very little hope of any treatment.*

He attended counselling and after some months felt able to use his skills to help others learn about HIV. Over the following five years he visited numerous schools, workplaces and clinics to talk about HIV and use his personal experience to educate others and destigmatise HIV. He remained well until 1994 when he got TB. This was successfully treated and he was able to go back to work. His health deteriorated again in late 1995 and he had a bout of pneumonia and recurrent abscesses. He continued to be active in the PLHA network and was always very well informed about the latest development in HIV treatments, particularly ARVs. He even arranged a meeting for PLHA groups where ARVs were extensively discussed as "hope for people with HIV". Not a single person at the meeting was on ARVs or had any likelihood of ever being so. John's health has continued to deteriorate and he is unable to work. Despite having given more than seven years of his life to educating people about HIV he is now unable to buy food let alone any medication.

Stephen*, a medical doctor, developed HIV related symptoms in January 1992. By March 1992 he was getting weaker, requiring frequent hospital admissions and by July he had to give up work. In February 1996 he was admitted in critical condition and remained unconscious for eight days. He was eventually discharged after three weeks reasonably well. It was then that he expressed the desire to try some of the antiretroviral drugs. He was counselled about the expense and possible side effects and decided to discuss it with the family. Initially his family discouraged him from spending such a large amount of money when had had a big family to look after. His decision was much swayed by the media stories about the protease inhibitors which were run during and after the Vancouver conference.*

In August 1996 he started on indinavir and ZDV only because he could not afford triple therapy. Indinavir had to be obtained from the USA through friends, costing him about $600 for a month's supply. He managed to acquire ZDV locally at a cost of $200 for a month's supply. By the time he started the combination therapy he was a very sick man. No basic tests such as CD4 cell counts or viral measurements had been done. After 2 months treatment he had a bad spell where he was taking the medicines irregularly either because he was vomiting or because he was taking too many other drugs. In January he went two weeks without indinavir because his supply did not arrive in time. He was getting it through people who were travelling to Uganda to minimise on courier expenses. When the medicine did arrive he resumed taking it but now he was getting weaker. He developed septicaemia and died on February 9th 1997 with the January bottle of indinavir hardly used.

Maureen *is a 28 year old single mother with two daughters, aged 3 and 5. Her husband, a police officer, died last year and his family took virtually all their possessions after the burial. "Property grabbing" is common. Maureen is a teacher and until recently was teaching the final year of primary school. With her take-home pay she was just about able to pay for the rent of her 2 room compound home and feed herself, the children and her younger sister who had come to live with her to look after the children whilst she was at work. Her house is not electrified and water is collected from a communal pump more than 100 yards from the house. She had an HIV test following her husband's death as she suspected that he had died from AIDS. He had widespread KS and eventually died of meningitis. Maureen's main concern is the future of her children. Whilst she was working, life was tolerable but now that she is too weak to work she cannot support her family. Her sister has been forced to sell sex merely to get enough money to feed them all. Maureen is aware of the "wonder drugs" that are available for people with HIV. She has read about them in the newspaper. Her concern is how can she feed her children and she is anxious about who will look after them when she dies.*

Anthony*, a relatively successful banker came to the company clinic after a loan to build a house for his wife and new son had been refused on medical grounds. After much heartache, he decided to be tested for HIV and found that he was seropositive. His wife was also tested and was seronegative. He wanted the doctor to get hold of antiretrovirals whatever the cost. As he earned approximately $1000 a month he could put his entire salary into ARVs or build a house for his wife and new son. He decided to build the house and start ARVs only when he became immunocompromised. He remained well for 3 years and built his house.*

By late 1995 his CD4 count had fallen to 160 and he started on ZDV and ddI. His CD4 remained stable until March 1997 when he had a severe attack of herpes zoster. He was prescribed high dose acyclovir and he made a quick and complete recovery. But by June 1997 his CD4 had fallen further. He badgered his doctor to change his regimen to include a protease inhibitor. Through an American mail order company the doctor managed to obtain indinavir at 50% the local cost. He started on triple therapy and by October his CD4 count had risen to 380 and he was remarkably well.

His "success" must in part be due to his wife. She kept him to his regimen religiously. She dealt with her own stresses in resigning herself to only one child in the face of extreme pressure from relatives (who do not know her husband is HIV-positive) to have more children. How long his good health will continue is anyone's guess.

Foreword

1996 and 1997 were marked by fresh optimism about finding a solution to the devastating problem that HIV/AIDS has come to represent - in terms of serious social and economic disruption and appalling human suffering. This new hope came from the development of a growing number of new approaches that promise a longer life, of higher quality, supported medically and socially, for people living with HIV infection. The development of new antiretrovirals (ARVs), particularly the combination therapies of three ARVs including one protease inhibitor, has been greeted with enormous enthusiasm.

WHO, in collaboration with UNAIDS, responded to these important developments with an Informal Consultation on the Implications of Antiretroviral Treatments, held in April 1997 in Geneva. As an immediate follow up to the Consultation, a set of guidance modules has been prepared for decision makers at health planning units of government ministries, major hospitals, and academic and training institutions, on major issues relating to antiretroviral treatments.

The majority of people living with HIV/AIDS in developing countries have no access to these costly treatments - they will perhaps obtain a couple of courses of antibiotics to treat opportunistic infections when these arise and if they are lucky, pain killers in the last stages of disease. Many people living with HIV/AIDS learn about the new treatments through the media, are filled with hope and prepared to mobilise whatever financial resources are needed to obtain the drugs as soon as possible. Medical requirements to ensure that the treatment can be prescribed safely and effectively may be scarcely considered. How to pay for the drugs on a long term basis and the impact on the family of devoting all resources to buying drugs are likewise secondary considerations, perhaps to be dealt with “tomorrow”.

UNAIDS and WHO are committed to increasing access to new technologies which have been shown to be effective in preventing and treating HIV/AIDS and improving length and quality of life, to all those in need. We share the general enthusiasm about the remarkable advances in ARV treatments. But this enthusiasm is tempered by two major concerns: one, is their long term benefit - and only clinical experience over several years at least will provide evidence that a reliable, long term treatment has been found. The other is the accessibility of these expensive and difficult treatments to the vast majority of the world’s HIV infected people, namely those living in the developing countries where resources for health care are often very limited.

New compounds are being synthesised and developed at a tremendous rate. It is our hope that cheaper and easier treatments will become available in the near future. Meanwhile, UNAIDS and WHO will regularly assess progress and disseminate information on the state-of-the-art of the new treatments, and promote and facilitate access to the drugs to all in need, through advocacy with national governments and the pharmaceutical industry, and through their international networks of researchers, health professionals, and NGOs. The guidance provided in these modules will be regularly updated to keep up with the latest advances.

Brief history

Since the human immunodeficiency virus (HIV) was first identified as the cause of AIDS, enormous research efforts have concentrated on identifying and developing compounds to suppress its replication.

In 1987, zidovudine (ZDV, formerly known as AZT) was approved by the US Food and Drug Administration. In the years that followed, four other drugs of the same family were introduced. The principal problems with these drugs, including ZDV, is their limited potency, their toxicity and their time-limited benefit - largely due to the development of resistance.

Large multicentre clinical trials then showed that double therapy with two of these drugs was superior to monotherapy in terms of disease progression and survival. Greater and more sustained decreases in plasma levels of HIV-1 RNA were achieved with double combinations.

Significantly larger reductions in viral load were achieved by adding a new class of agents, the protease inhibitors, which became available in early 1996. Over the past two years, the number of antiretroviral agents available has expanded substantially and trials of the new antiretroviral treatments, particularly the triple therapies using combinations of drugs from different classes have shown impressive short term results decreasing both morbidity and mortality and offering real hope for people living with HIV/AIDS of a longer and a better life. Consequently, combination therapy has rapidly become the gold standard of care in antiretroviral therapy.

With regimens of three drugs, over three quarters of HIV-infected patients had levels of virus in plasma suppressed to below the level at which it could be detected and this persisted throughout follow up for as long as one year in ARV naive patients with good adherence.

It is now recognised that the sustainability of the therapeutic response to ARVs depends on the level of suppression of viral replication. Regimens which only partially suppress replication will ultimately promote the emergence of resistance. The aim of therapy therefore is the full suppression of replication to below detectable levels by the most sensitive assays available. In practical terms, this implies today the use of triple therapy usually including a powerful protease inhibitor.

The latest research shows that even with sustained suppression of HIV replication, there are still reservoirs of HIV in patients under treatment. Furthermore, the virus recovered may not be latent but still replicating at a slow rate. Viable virus has been retrieved from patients who have been well suppressed on tritherapy for up to two years. Patients who are well controlled with undetectable viral loads show massive rebound viremia when for some reason (such as an accident) they suddenly stop taking ARVs.

Recent studies are reporting high levels of resistance in relatively short periods of time, even with good adherence to the regimen. Resistance develops more readily in patients who have already received ARVs and in those with low CD4 counts. The most favourable results have been obtained from studies in patients with optimal adherence. It is likely that treatment failure in normal clinical practice will be higher.

In recognition of these limitations, researchers are already seeking alternatives to triple therapy - quadruple therapy and new classes of drugs. Approaches to HIV treatment are in rapid evolution as work continues on disease pathogenesis and viral dynamics.

Critical issues in ARV treatments for HIV infection still require clarification: when to start and change treatment, and with which combinations, what drug sequence strategy to adopt. With the rapid progress in drug development, treatment guidelines are likely to have to be frequently updated.*(For current recommendations on the use of antiretroviral treatments see Module 4)*

The use of zidovudine to *prevent* mother to child transmission of HIV was shown as long ago as 1994 to be effective (reducing transmission by 50-70%). Monotherapy for the *treatment* of HIV infection is now regarded as obsolete because of serious problems of resistance.

ARVs are also used in post-exposure prophylaxis for health care workers (See Module 7). Guidelines have been developed in industrialised countries all of which recommend ARV therapy following accidental exposure to blood which may be contaminated by HIV. It should be noted that data on efficacy is limited and that the average risk of seroconversion following exposure, even without treatment, is very low. Minimising risks of exposure through strict observance of universal precautions remains the priority.

Treatment for the few: but a concern for all

The major challenges in antiretroviral treatments are access, correct and supervised use, adherence and the development of resistance. The new treatments are not available to the vast majority of the world's HIV infected people, most of whom live in the developing countries. Triple therapy is very expensive and the related services required to ensure their safe and effective use are complex. Adherence requires a strict individual protocol and reliable psychosocial and material support.

Despite this, ARVs are present in most poor countries of the world, but accessible to a very small, and in the main, wealthy, minority. Efforts to obtain the drugs, often in an irregular and haphazard fashion, may absorb the entire resources of the family. In these situations, problems of incorrect and unsafe use, unreliable supply, and a black market in both good quality and counterfeit drugs are likely to appear. This has serious public health implications because of the almost certain development and spread of resistant strains. It is therefore urgent for policy makers, ministries of health, health professionals and NGOs to address all aspects of ARV treatments including access, irrespective of the wealth and circumstances of their country.

Over and above the public health concern, UNAIDS, WHO and its member states are committed to the principle of universal access to effective treatments for all in need. All efforts therefore will be made to assess the currently available treatments, the desirability and feasibility of introducing them into national health systems in different settings, and likely future research developments; to increase access to these treatments, to press for further research into cheaper and easier regimes, to negotiate with industry to devise mechanisms to reduce prices; and to maintain and reinforce prevention and care activities for all those affected by HIV/AIDS.

In response to requests from people living with HIV/AIDS, health professionals and governments, WHO held an informal consultation on the implications of antiretroviral treatments in April 1997, in collaboration with UNAIDS. Participants included clinicians, researchers, PLHA, national AIDS programme managers, representatives of ministries of health, the pharmaceutical industry, NGOs, donors, UNAIDS, other UN agencies, and various WHO programmes. A report of the consultation* was produced in September 1997 and French and Spanish versions will be available in early 1998. The report summarised the essential points raised during the consultation and derived from discussions, presentations and background papers. The essential points raised during the consultation are summarised below; the full report is available from Distribution and Sales, WHO, 20 Avenue Appia, 1211 Geneva 27 (fax: 41 22 791 4857; email: publications@who.ch) or from UNAIDS Information Centre, 20 Avenue Appia, 1211 Geneva 27 (fax: 41 22 791 4187; email unaids@unaids.org).

Technical guidance modules

Audience

The modules are addressed mainly to "middle level" decision makers at academic and training institutions, major hospitals and district hospitals. However, in all modules there are issues which may be of concern to technical decision makers in government ministries such as health, planning or finance.

Topics

Key content areas for the modules were identified from the issues raised and discussed at the consultation. The nine guidance modules which make up the complete set are:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into health systems: economic considerations
3. Antiretroviral treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to the human immunodeficiency virus
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

The modules form a complete set which together address the major issues relating to the use and provision of ARVs but each is designed to "stand alone". Depending on further developments in the treatments and experience with their use in different settings, there may be requests for guidance in other areas. Other modules may then be added to the set.

** The Implications of Antiretroviral Treatments: Informal Consultation, Geneva, April 1997. Edited by Eric van Praag, Susan Fernyak and Alison Martin Katz*

Summary of the Report of the WHO Informal Consultation on the Implications of Antiretroviral Treatments

Aims:

- To review the findings on ARVs - their efficacy, side effects, problems of resistance , adherence and cost benefits;
- To discuss minimum requirements for their safe and effective use;
- To examine the clinical, social, financial and ethical implications of providing ARVs, especially in low and middle income countries;
- To make preliminary recommendations.

Currently available antiretroviral drugs

Current antiretroviral agents for HIV/AIDS can be divided into **two major classes of drugs**: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs are further divided into nucleoside (NRTI) and non-nucleoside (NNRTI) subclasses. A third class, integrase inhibitors, is under development, as are drugs with other mechanisms of action (e.g. hydroxyurea, chemokines and interleukin 2).

Eleven antiretroviral agents are currently available in different parts of the world. Registration of drugs differs from country to country. Ten of these agents have been shown to be useful in the treatment of HIV/AIDS by slowing the progression of the disease and prolonging survival. Table 1 lists the currently available agents, by brand name, class and estimated market cost, based on US pricing in June 1997.

Table 1

Generic Name	Brand name*	Class	Unit dose	Cost: Three months/US$**
didanosine (DDI)	Videx	NRTI	100 mg	420 - 700
lamivudine (3TC)	Epivir	NRTI	150 mg	690
stavudine (D4T)	Zerit	NRTI	40 mg	700 - 730
zalcitabine (DDC)	Hivid	NRTI	0.75 mg	630
zidovudine (ZDV)	Retrovir	NRTI	100 mg	720 - 860
indinavir	Crixivan	PI	800 mg	1350
nelfinavir	Viracept	PI	250 mg	1670
ritonavir	Norvir	PI	600 mg	2080
saquinavir	Invirase	PI	600 mg	1720
delavirdine	Rescriptor	NNRTI	100 mg	
nevirapine	Viramune	NNRTI	100 mg	740

***brand names may vary between countries**
**** ranges reflect dosing variations**

Best treatment option available

Evidence has shown that a combination of ARVs including at least one PI, is the most effective treatment available to suppress the replication of HIV. This is reflected clinically, in decreased incidence of opportunistic infections, decreased hospitalisations and ability to return to normal functions of daily living. Serologically, it is reflected in decreased viral loads (often to undetectable levels) and increases in the number of CD4 cells.

Cautious optimism

As yet it is not known how long these benefits will last. Long term clinical outcomes (spanning several years of observation) have not been demonstrated; resistance may occur even with triple therapy, and "sanctuary" sites may exist where drugs cannot suppress viral replication even in individuals under treatment. In addition, when treatment is interrupted, viral rebound may occur leading to rapid clinical deterioration. Finally, in only a proportion of patients on triple therapy, with available techniques, is viral load reduced to undetectable levels.

The combination therapies are very expensive (US$ 1000-1500 per month in May 1998) and require a rigorous and difficult daily regimen in order to avoid the emergence of drug resistance. Fifteen to twenty tablets are to be taken over the day. Unpleasant side effects are common, drug interactions have to be considered, and clinical and laboratory monitoring is required to detect adverse reactions.

Individual needs and public health considerations

During the consultation there was a shared understanding that ARVs can improve the life prospects of PLHA and that combination therapy represents the best treatment option available currently. Participants recognised the primacy of the need to respond to the individual suffering of PLHA while acknowledging concerns about long term sustainability and safety of ARVs, and responsibilities for the health needs of the general population.

Guiding principles

- Universal access to care and treatment, a principle which WHO promotes as a human right, is the ultimate aim. The fact that access might not be achieved immediately and universally does not preclude progressive introduction of ARVs, recognising that they are already present in countries. The stark contrast between industrialised countries where patients are usually receiving these treatments through public and private insurance schemes and developing countries where the majority of those requiring treatment cannot access these drugs, is ethically unacceptable.

- As an overarching ethical principle, it must be recognised that combination ARV therapy with at least 3 ARV currently represents the most advanced therapy of choice for people living with HIV/AIDS. There is therefore an obligation for governments to make every effort to increase access to these treatments within the context of national health programmes which address competing health care needs. Governments must ensure non-discrimination and equity in access among PLHA and among those living with other life-threatening conditions requiring comparably costly and complex therapies.

- The provision of ARVs must not divert resources from HIV prevention activities (e.g., control of STDs, promotion of safer sex including condoms, and ensuring a safe blood supply), the treatment of opportunistic infections, and research to develop preventive tools, particularly vaccines and microbicides. Neither should it divert resources from other essential public health programmes.

- ARV treatments must be supported by a functioning health and social system which ensures adequate diagnosis and treatment of opportunistic infections, appropriate pain management, and correct use of and adherence to ARVs to avoid the emergence of drug resistance and transmission of resistant strains.

- Adherence is a required component of effective treatment, not a precondition for access to treatment. Patients should not be excluded *a priori* from ARV treatment because they belong to groups regarded as unlikely to adhere (e.g. injecting drug users, the homeless and the poor). Health providers' roles and responsibilities in ensuring adherence must also be recognised.

- The supply, distribution and provision of ARVs require national quality assurance systems to be in place. Governments have a regulatory and supervisory role in these areas

- Cost is a major issue. Collaboration between and within countries to enable those who are most in need to obtain treatment, should be promoted and mechanisms/strategies put in place to effect such solidarity. It is ever more urgent for governments to reconsider the level of the health budget in relation to the budget for other sectors.

- Commitment to continue basic science research into drugs and clinical outcomes is essential as none of the currently available ARVs are ideal and a number of promising drugs are under development.

- The pharmaceutical industry is a key partner in health care, and has social responsibilities as do all civil organisational and institutional bodies. Their collaboration is essential.

- Prevention and care are two sides of the same coin. All prevention efforts reduce or limit the final number of infected people needing care. Whenever care is provided, there is a golden opportunity to provide or reinforce prevention education.

Minimum requirements

- Availability of reliable, inexpensive tests to diagnose HIV infection and access to sites providing voluntary and confidential counselling and testing.

- Adequate management of opportunistic infections including availability of affordable drugs for their treatment and prophylaxis.

- Laboratory facilities to monitor adverse reactions including liver function test, complete blood count, amylase, and electrolytes.

- Appropriate training for clinicians and nurses in the correct use of ARVs.

- Support of a social network to help patients adhere to the regimen.

- Strengthening of health and social services in a continuum of care, from the home, through community health centres, to district/city hospitals, with flexible and timely referral and co-ordination procedures; provision of material and psychosocial support for those taking ARVs at various levels of the continuum,

- Reliable, long-term and regular supply of drugs at the health centre level.

- Joint decision making between physician and patient on all aspects of ARV treatment, including the decision to begin ARVs.

Recommendations

- Long term affordability based on scenarios which assume full coverage and total adherence is not achievable at present in most countries. A useful approach might be to ensure access at a limited number of centres of excellence where clinical, laboratory and social support can be guaranteed. Allocating different therapies to subsets of people with HIV-related conditions (e.g. ARVs for prevention of MTCT and PEP), taking into account the realities of different settings, may represent a rational strategy offering affordable starting points.

- Because of the high daily turnover of virus production, resistant strains develop very easily. Strict adherence to the drug regimen is therefore essential. Emergence of resistance should be carefully monitored through a network of collaborating laboratories. WHO/UNAIDS could establish such a co-ordination mechanism.

- In order to minimise unregulated supply and distribution leading to irregular provision, unsupervised use and the emergence of resistance, there need to be effective national drug regulatory authorities.

- The diagnosis and treatment of opportunistic infections remains an essential component of the clinical management of HIV/AIDS patients. As in the recent revision of the WHO essential drug list in December 1997, governments should also consider adding drugs for

opportunistic infections, other HIV-related conditions and pain management to their Essential Drugs Lists.

- International technical agencies and programmes should collect and widely disseminate information on all aspects of ARV treatments including the drugs themselves, rational approaches to problems of adherence and resistance, prescription guidelines, health system requirements, pricing policies and financing options.

- Clinical studies in all countries should follow a basic set of ethical guidelines. All clinical trials should aim to provide meaningful estimates of the gain in quality-adjusted life years, reflecting not only changes in survival but also improvements in the quality of life.

- The currently available nucleic acid amplification assays (DNA and RNA) used to measure viral load are not equally sensitive and/or equally efficient in amplifying all known HIV subtypes. The tests need to be improved to allow accurate detection of the HIV variants most prevalent in Africa, Latin America and Asia. The standardisation of these assays is also an urgent priority.

- Viral load measurement is highly desirable to monitor efficacy of ARV treatments in asymptomatic patients.

- Operational research on how best to implement ARV treatments in settings where resources are limited and adherence beset with difficulties, is needed in low and middle income countries.

- Training of health professionals in the correct use of ARVs is essential if the decision to introduce them is made. Clinical guidelines should be developed for professional use. Training should be undertaken to reach all care providers as a team.

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

Office of AIDS and Sexually Transmitted Diseases (ASD)
World Health Organization
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4613
Fax: 41 22 791 4834

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WHO/ASD/98.1

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Distr: General

Guidance Modules on Antiretroviral Treatments

Module 2
Introducing Antiretroviral Treatments into Health Systems: Economic Considerations

Joint United Nations Programme on HIV/AIDS (UNAIDS)

World Health Organization (WHO)

WHO/ASD/98.1

UNAIDS/98.7

Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Katherine Floyd and Dr Charles Gilks, Liverpool School of Tropical Medicine, UK, for preparing the text of this module;

Dr Thierry Mertens, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, Dr German Velasquez, Action Programme on Essential Drugs, WHO, and Dr Joe Kutzin, Division of Analysis, Research and Assesment, WHO, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for coordinating the project.

Module 2
Introduction of ARV Treatments into Health Systems: Economic Considerations

Introduction

This module is structured in seven main sections, which are:

- **Affordability (1)**, in which cost, GNP, health expenditure and HIV prevalence data from various parts of the world are presented to illustrate how it is possible to assess whether ARVs are affordable at national, regional, district or institutional level, and in which suggestions for how to make similar assessments for individuals/ households are made. Ways in which ARVs may be made more affordable are also discussed;
- **Cost-effectiveness (2)**, in which existing evidence that can be used to assess whether or not ARVs represent a good investment of public resources is provided, problems with the application of cost-effectiveness analysis to ARV treatments are described, and reasons why governments and social insurance schemes may decide that financing ARVs is worthwhile even if they do not appear to pass the test of "cost-effectiveness" are explained. Ways in which the difficulties with cost-effectiveness analysis can be reduced are also suggested;
- **Availability of necessary human/physical resources (3)**, in which the importance of assessing whether the inputs needed for provision of ARV treatment are actually available or mobilisable is discussed;
- **Equity (4)**, which addresses the issue of who is most likely to benefit from ARV treatment, using some preliminary evidence from Côte d'Ivoire and Mexico. This emphasises that the likely distribution of resources is an important issue to consider with ARV treatments, and has particular implications for financing policy;
- **Financing (5)**, in which the main options for funding ARV treatments are assessed, including public funding, social and private insurance, user fees/other out-of pocket payments, donor agencies and community financing. This section draws on the analysis of issues of affordability, cost-effectiveness and equity in (1), (2) and (4);
- **Provision (6)**, in which the potential role of different health care providers in delivery of ARV treatments is analysed; and
- **ARVs, economics and health sector reform (HSR) (7)**, in which the interactions among various aspects of HSR, economic issues, and the introduction of ARVs are considered. Although some of these are touched upon in earlier sections, the importance of HSR initiatives merits a separate discussion.

Figure 1 summarises how these issues relate to decision-making on ARV treatments. However, sometimes, the answers to questions 1,2 and 3 are not simply yes or no. ARVs are likely to be affordable to some, but not to all. The bullet points illustrate the most important considerations in each case.

When using this module, it is important to bear in mind that there are large differences between countries, regions, communities and individuals in terms of the AIDS epidemic and in terms of many socio-economic factors. The module provides a range of examples from Latin America, sub-Saharan Africa, the Caribbean and Asia which highlight these differences. Evidence is limited at present and at this stage it may only be possible to propose general principles rather than specific guidance.

1. Are ARVs affordable?

- Estimate the numbers of people eligible for ARV treatment (a) for all indications and (b) for three main indications: treatment for all those HIV+/those with AIDS; MTCT; PEP for health workers
- Compare the cost implications of providing treatment to all those eligible with GNP, health expenditure, and the public sector health budget. What % of these would expenditure on AR treatment provision represent? For National Insurance Schemes/Social Security Agencies, compare the annual funds available with the likely costs of providing different treatment indications to fund members
- Assess affordability at individual/household level using cost and income distribution data

→ **NO**

↓ **YES**

2. Is ARV treatment cost-effective i.e. a good investment of resources?

- Compile evidence on cost-effectiveness of ARVs; model cost-effectiveness if necessary
- Compare estimates of ARV cost-effectiveness with those for "accepted" health interventions. Focus on the most directly relevant comparisons e.g. other maternal and child health interventions in the case of MTCT
- Assemble evidence concerning what is currently spent on HIV/AIDS care and prevention. U this to assess the "opportunity cost" of ARV treatments i.e. what other types of HIV/AIDS prevention and care could be provided with the expenditure likely to be required for ARV treatment? This analysis will illustrate what benefits may be given up by investing in ARV treatment
- Use analysis to assess whether ARVs are likely to represent a good investment of public/grou (e.g. NI scheme; social security organization) resources, or whether ARV treatment is more appropriately provided on the basis of willingness-to-pay

→ **N O**

↓ **YES**

3. Are the human/physical resources necessary for ARV treatment provisio available; if not can they be mobilised?

- Are drug supply systems operating sufficiently well?
- Are the right staff available (e.g. counsellors, physicians, lab staff, pharmacists, managers)? not can they be recruited? Is training available?
- Are laboratory facilities adequate for monitoring treatment & side effects?

→ **NO**

↓ **YES**

4. What are the equity implications of ARVs and are these acceptable?

- Who will access ARV treatment is practice?
- is this equitable/acceptable? what are the implications for financing policy?

↓ **YES**

5, 6,7. Who should finance and provide (supply) ARV treatments? How do these decisions relate to HSR?

- Government: (financing options = increased taxation, budget re-allocation, efficiency-saving combination of subsidy and user fees)
- National Insurance Schemes/Social Security Agencies
- Donor agencies
- NGOs/voluntary sector
- Private sector: private insurers, private practitioners/clinics/hospitals, companies
- What mix of these might be appropriate?
- with HSR, consider issues of decentralisation, focus on policy setting/monitoring/ regulation national level, promotion of private sector, new financing mechanisms

1. Affordability

Affordability is a continuum, not an absolute yes or no. It can be assessed from a number of perspectives, including that of:

- a country
- a region
- a district
- an individual/household
- an institution, such as a national insurance scheme or a social security organisation.

This section presents both cost data and a methodology for using these cost data, which in combination can be applied to assess the affordability of ARV treatments at each of these levels. It also discusses whether ARV treatments could result in some cost-savings, and suggests how ARV treatments may be made more affordable in future.

1.1 The cost of ARV therapy

The costs of providing ARV therapy fall into two major categories:
(a) drug costs; and
(b) costs associated with safe and effective use.

Table 1: Anti-retroviral drug costs (US$) at market prices in 1997

Drug and dosage required	Monthly Cost	Annual Cost[1]
zidovudine (ZDV) 250 mg twice a day	228	2 738
didanosine (DDI) 200 mg twice a day	175	2 102
zalcitabine (DDC) 0.75 mg three times a day	220	2 640
stavudine (D4T) 40 mg twice a day	232	2 788
lamivudine (3TC) 150 mg twice a day	214	2 572
ritonavir 600 mg twice a day	692	8 308
saquinavir 600 mg three times a day	545	6 540
indinavir 800 mg three times a day	533	6 400
nevirapine 100 mg twice a day	272	3 260
Double combination therapies	403 to 773	4 836 to 9 276
Triple combination therapies	662 to 993	7 944 to 20 224

The costs of the drugs are shown in Table 1. These are largely derived from USA sources, so it is important to note that under market *conditions the costs of drugs may be significantly higher in developing countries*. Double combination therapies range in costs from US$ 4836 to US$ 9276 per year, while the triple combination therapies range from US$ 7944 to US$ 11916, increasing to up to US$ 17,580 if ritonavir is added. *Country-specific data on these costs needs to be assembled wherever possible*.

Data concerning the other important costs associated with providing therapy are shown in Table 2. These include: HIV tests to establish whether someone is HIV-infected and hence eligible for therapy; pre- and post-test counselling; regular out-patient visits to monitor patients for side-effects and to issue supplies of drugs; laboratory tests such as CD4 counts, complete blood counts, viral loads, and chemistry panels to monitor patient health status;

[1] World wide web page of AIDSRx, 1997

and out-patient visits/hospitalisations associated with adverse drug effects. Again, *country-specific data on these costs should ideally be assembled* since they will allow more accurate assessments of affordability to be made.

Table 2: Non-drug costs associated with antiretroviral therapy (US$)

Cost Item	Unit Cost[2]
CD4 cell count	30-157
Viral load test	133-163
Complete blood count	2-21
Chemistry panel	12- 35
Serum amylase	18
Transfusion for ZDV-induced anaemia	580
HIV ELISA test	3-6
Rapid HIV Test (Capillus)	3
Rapid HIV Test (Abbot)	10
Pre-test/post-test counselling visit for HIV-person	22/33
Pre-test/post-test counselling visit for HIV+ person	22/77
Test + counselling	18/12
Out-patient visit (N.B. This is an average OPD visit cost, not specific to ARV therapy-related)	17-120

It is worth emphasising that in addition to the costs shown in Table 2, some developing countries' laboratory services may have to be strengthened considerably (including substantial investment in quality assurance) if they are to be capable of providing the diagnostic and monitoring support necessary for provision of ARV therapy (see Module 5). Developing such capacity may have large costs attached to it. It is also possible that there will be costs associated with either basic or specialised in-service staff training.

1.2 A methodology for assessing whether or not ARVs are affordable

There is no "right" way to assess affordability. Two approaches are described here. The first applies to affordability at a level beyond the individual or household, and is thus relevant to assessing affordability at national, regional, district or insurance institution level. The second applies to affordability at the level of the individual/household, and is thus relevant to both financing policy on ARVs and considerations of equity (see also sections 4 and 5). If ARVs are not affordable at an individual/household level, public funding or insurance coverage will be necessary if ARVs are to be made widely available, rather than accessible to a small, relatively wealthy minority of the population only (see also section 5).

Affordability at national, regional, district or insurance institution level

Three key pieces of information are needed to assess affordability at either national, regional, district or insurance institution level. These are:

- **how many people in the country/area/institution are eligible for ARV treatment?** The numbers should be defined over a specified time period, usually a year. Numbers

[2] Source recent literature and worldwide web on AIDSRx

can be assessed (a) overall, for all indications or (b) separately for the three major indications - MTCT, PEP, all HIV+ individuals/people with AIDS;

- **what is the likely cost per person for ARV treatment?** Again, this needs to be specified for a particular time period or episode. A year would be appropriate for treatment of all HIV+ people/people with AIDS; one episode of treatment would be appropriate for MTCT and PEP;
- **what are the total resources available per year in the country/district/region/ institution?** This can be measured in terms of (a) total income (GNP for a country as a whole, with a similar measure of total wealth also relevant to regions/districts; total value of annual contributions for an insurance scheme) (b) existing health expenditure (c) total annual drug expenditure and (d) total spending on HIV/AIDS prevention and care. For a country, region or district, it may also be relevant to consider total public sector health spending. This is because if ARVs are found unlikely to be affordable at individual/household level, the affordability of public sector funding will need to be considered in its own right.

These pieces of information can be used to assess how the likely total costs of ARV treatment compare with available resources, in turn allowing conclusions concerning affordability to be drawn. Such an assessment, for ARV treatment for all HIV+ people, is illustrated at national level for a number of countries in the table below. However, *the same analytical principles apply equally to the other levels too, and to other indications for ARV treatment.*

Assumptions are likely to be needed in such analyses, and the analysis illustrated below is no exception. It is important to be explicit about these assumptions, because this enables the implications of changed assumptions (e.g. the numbers eligible for treatment, the cost of drugs) to be explored as a key part of an assessment (see also section 2 on the role of sensitivity analyses in cost-effectiveness studies). In the illustrative analysis below, the assumptions are:

- the annual cost of therapy is approximately US$10 000, which includes both drug costs and the cost of other inputs identified in Table 2 (more accurate assessments should be possible when performing such an analysis for a specific country); and
- all HIV+ people are eligible for treatment.

It is also worth highlighting the fact that the data in Table 3 are out-of-date, and this may be a problem common to many such analyses. It is almost inevitable when a common source is used (in this case "AIDS in the World II[3]"), because it is time-consuming to compile data for all countries. However, if the principles illustrated here are applied in 1998 or at a later date within a particular country/region/district/ institution, it should be feasible to incorporate more up-to-date figures.

The countries have been chosen to show how the affordability of ARV treatments is likely to depend critically on two factors:

- the **magnitude of the HIV/AIDS epidemic** (the numbers of people with HIV); and
- **income levels**.

It is clear, for example, that ARV treatment is much more affordable in Latin America and Asia than it is in sub-Saharan Africa. This reflects the fact that in Latin America and Asia

[3] AIDS in the World II, 1996 eds. Mann J and Tarantola D.

the HIV seroprevalence is currently *relatively* small, and that Latin American and at least some Asian countries (e.g. Thailand) have much higher overall levels of income. In turn, this helps to explain why several Latin American governments or social security schemes in Brazil, Mexico, Costa Rica and Uruguay have been able to decide to finance ARVs, why Thailand is publicly funding ARVs to some extent, and why there is virtually no public funding of ARV treatment in sub-Saharan Africa. It also shows that countries at similar average income levels (e.g. Bangladesh and Uganda) can have very different capacities to afford ARVs because of substantial differences in the magnitude of the HIV/AIDS epidemics.

Table 3: Affordability assessment for a range of countries

Country	Number of HIV+ adults 1994 (% total adult population)	Estimated Ann Cost of ARV treatment (US$ billions)	GNP in 1994 (US$ billions	Cost of ARV treatment as % of GNP	Cost of ARV treatment as % o total health expenditure
Ghana	172 000 (2)	1.7	7	24	600
Uganda	1 300 000 (15)	13	4	325	8 125
Zambia	700 000 (17)	7	3	233	5 825
S. Africa	650 000 (3)	6.5	125	5	125
Cote D'Ivoire	390 000 (7)	3.9	7	56	1 400
Thailand	700 000 (2)	7	130	5	125
India	1 750 000 (0.5)	17.5	279	6	150
China	10 000 (0.002)	0.1	630	0.02	<1
Bangladesh	15 000 (0.03)	0.15	27	0.6	15
Trinidad	6 000 (1)	0.06	5	1	25
Barbados	4 000 (3)	0.04	2	2	50
Brazil	550 000 (1)	5.5	536	1	25
Costa Rica	9 000 (0.5)	0.09	8	1	25
Peru	30 000 (0.3)	0.3	44	0.7	18
Uruguay	5 000 (0.3)	0.05	15	0.3	8

The example above is for the most expensive indication for ARVs, and it is based on the assumption that all those HIV+ are eligible. In practice it is likely that far less than 100% of those HIV+ will come forward for treatment even if it is available, so that this could be seen as a worse-case scenario. On the other hand, unless the epidemic has already stabilised, the numbers of people infected are likely to increase for some years to come.

It is also worth emphasising that ARVs for MTCT and PEP are relevant to much smaller numbers of people, and that they are less expensive. It is therefore conceivable that while ARV treatment for all those HIV+ may not be affordable in a given area/institution, these two indications may well prove affordable. ***It is thus critical to assess all three indications, and to assess them separately***. For example, in Thailand it has been estimated that an MTCT intervention would consume only 20% of the National AIDS programme budget, making it appear relatively affordable (Prescott, 1997).

A second example of an affordability assessment is provided in Table 4 below, which shows the proportion of the national drug budget which would be accounted for by different ARV treatment indications in a variety of countries.

Table 4: Estimated annual ARV drug costs as a percentage of total annual public drug budget

Country	MTCT	AIDS triple therapy	Treatment of HIV+
Argentina	0.1	2	5
Colombia	0.2	7	14
Brazil	0.2	16	18
Sri Lanka	0.2	8	15
Philippines	0.6	16	31
Thailand	5.3	357	526
Guinea	18.0	349	692
Zimbabwe	35.0	616	1221
Cote d'Ivoire	70.6	906	1796

Affordability at individual/household level

At the level of the individual or household, a useful way to assess affordability is to consider:

- what level of individual/household income is required to make purchase of ARVs affordable?
- how many people fall into those income bands which enable purchase of ARVs?

It is important to remember that the totality of an individual/household's income will not be available for health care. Some basic needs e.g. food will always need to be paid for. It is the individual/household's discretionary expenditure - the expenditure available once basic needs have been met - that is of most relevance. If this level can be estimated, and if income distribution data are available, it should be possible to assess what proportion of the population could realistically pay for ARV treatment themselves. In turn, this will be useful for informing financing policy (see section 5). For example, in a recent assessment for Thailand, it was estimated that 50% of the population could afford ARV treatment for AIDS at the subsidised price of US$500 per year.

1.3 Could ARV treatments be cost-saving?

Providing treatment to people with HIV-related health problems e.g. tuberculosis may be associated with high costs. If ARV treatments prevent some of these problems, they will result in some cost-savings. In developed countries such as the USA, there is some evidence that the costs associated with AIDS patients may be so high that ARV treatments result in net cost-savings, particularly when indirect costs (i.e. the costs associated with lost income due to ill-health or premature death, as opposed to direct costs which are those associated with provision of health care) are considered. For example, the average wage of a US citizen is much higher than the annual cost of ARV treatment. It is easy to see how the costs of ARV treatment could be outweighed by the monetary benefits resulting from such treatments, if ARV treatment allows someone to remain healthy enough to work. The high costs of paediatric AIDS care also appear to make MTCT cost-saving in the USA.

In developing countries, cost-savings are much less likely to result from ARV treatments. It has been recently estimated that AIDS care costs approximately 1.5 times GNP/capita (Sheperd et al, 1997), and this is in line with earlier summaries of cost estimates (Martin, 1996; see Table 5 below). Pre-AIDS care is likely to cost less. This means that even if ARV treatments prevented HIV-related illness altogether, they would certainly not be cost-saving for the health system in any country with an average income of below US$ 7300 (given that ARV treatment costs approximately

US$ 10,000 per year).

Table 5: Costs of medical care for AIDS patients in different countries

Country	Cost per year of medical care	% of per capita GDP
Thailand	$1000	47%
Sri Lanka:- Low	$290	48%
High	$1060	177%
Malawi	$170	124%

Even if indirect costs are considered, a country would need to have an average annual per capita income of at least US$4 000 to make ARV treatments cost-saving (savings resulting from avoided illness would then be US$4 000 in wages and US$6 000 in health care costs per year). Moreover, over the long-run the figure may be higher, given that saved treatment costs only apply over the expected lifetime of HIV infection in the absence of ARV treatment, whereas it is likely that ARV treatments have to be undertaken over a more extended time period.

Overall, this means that ARV treatments are not likely to be cost-saving, on average, in developing countries. However, this should not conceal the fact that *for some individuals ARV treatments are likely to be cost-saving*. For the highest income earners in any developing country, annual income will exceed the costs of ARV treatments. This has implications for the role of government in ARV treatment, particularly in the areas of financing and regulatory policies (see sections 5 and 7).

1.4 How may ARVs be made more affordable?

As drugs constitute approximately 90% of total per patient annual costs for triple combination therapy, making ARVs more affordable is dependent on achieving reductions in drug costs.

How might such reductions be achieved? One option is for governments to purchase drugs in bulk. Table 6 below shows the drug costs that have been negotiated in Uruguay on the basis of bulk-purchase.

Table 6: Drug costs (US$) in Uruguay when drugs are purchased in bulk

Drug	**Negotiated annual treatment cost**	**Annual treatment cost as % of market pric**
ZDV	776	28%
saquinavir	4 340	66%
ritonavir	5 528	67%
lamivudine	2 108	82%

This shows that annual treatment costs approximately two-thirds of those quoted above have been achieved for two of the drugs, and the cost of ZDV has been reduced to 28% of the 1997 US market price.

In addition to bulk-purchase arrangements, international partnerships among national governments, international organisations and drug companies may facilitate reductions in prices which enable the drug companies to earn reasonable profits so that research and development costs are recouped. For example, drug companies have recently announced a reduction in prices of ARVs for MTCT in developing countries.

Finally, it is important to note that over time companies may substantially reduce their prices - ZDV was reported to cost more than US$10 000 per year in the late 1980s but now costs much less (Table 1). Furthermore, as patents expire generic products will be produced at lower prices. *Affordability should therefore be periodically re-assessed*.

2. Cost-effectiveness

If ARV treatments are affordable, a second key economic consideration is their cost-effectiveness. Cost-effectiveness analysis is useful for deciding whether ARV therapies are likely to represent a good use of resources managed on behalf of a group[4] - for example, a country's population or the members of an insurance scheme. It is therefore particularly relevant to government decision-making, since governments allocate resources on behalf of large population groups. If the likely cost-effectiveness of ARVs compares favourably with that of standard, accepted health interventions - particularly public health interventions - there are strong grounds for providing them. If the cost-effectiveness of ARV therapies compares unfavourably, then it is harder (but not impossible) to justify their provision.

2.1 Evidence concerning cost-effectiveness of ARV treatments

Table 7 summarises current evidence on the cost-effectiveness of different ARV treatments. The Disability Adjusted Life Year (DALY) is used as the outcome measure as this allows comparisons between interventions for different kinds of health conditions.

Table 7: Costs and cost-effectiveness of ARV treatments

ARV Treatment	Cost/DALY (US$)	Place, Date of Data, and Source
Prophylaxis for HIV+ pregnant wome (076 protocol)	approx. 40-60 (depending on l expectancy)	Model for "a developing country", Mansergh et al 1996
Prophylaxis for HIV+ pregnant wome (Thailand study short course ZDV & months formula feeds) As above but no formula feeds	248 86-200	Model for low and middle income countries, Marseille 1998 Model for Hlabisa District, S. Africa, Wilkinson et al 1998
Triple-combination therapy for HIV+ patients	$8,000 - 12,000 (based on drug costs only + assuming therapy must be take for life)	1997, market prices quoted for AR drugs
ZDV for post-exposure prophylaxis	approx. $10,000	Allen et al 1992
Triple-combination ARV prophylaxis people exposed to HIV infection	approx. $15,000 (based on drug costs only, *assumed 100% efficacy*)	1997, market prices quoted for AR drugs

The figures in Table 7 show that *of the ARV interventions available, prevention of MTCT is the most cost-effective*.

2.2 Cost-effectiveness of other health interventions which are widely implemented

To enable comparison with other health interventions, examples of the cost/DALY for a wide range of health interventions are shown in Table 8 below. These are taken from

[4] It is important to distinguish this from decisions made by an individual, where use of available income is simply based on willingness and ability to pay.

Jamison et al, *1993 Disease Control Priorities in Developing Countries* [5] and a recent publication on the cost-effectiveness of improved STI treatment in Mwanza, Tanzania.

Table 8: Cost-effectiveness of a range of health interventions

Intervention	Cost/DALY (US$)
Polio + DPT immunisation	20-40
Measles immunisation	2-15
Targeted screening for leprosy	0.5
Food supplementation for pregnant women	25
Improved STI treatment [6]	10
Mass dosage of Vitamin A to children under 5	9
Iron supplementation to pregnant women	13
Food supplementation for pre-school children	70
Blood screening for HIV	1-250
HIV prevention using IEC campaigns	1-150
Public prevention package targeted at cardiovascular disease	150
Treatment for acute respiratory infections	20-50
Diarrhoea treatment with oral rehydration therapy	35-350
Tuberculosis treatment	3
Leprosy treatment	7
Malaria: treatment of passively detected patients	200-500
Rheumatic heart disease treatment	100-200
Maternal and perinatal health	30-250
Cancers	2600 - 12000
Insulin-dependent diabetes	240

The most obvious benchmark for comparison is the cost-effectiveness data from the Mwanza study of improved treatment services for STIs in preventing HIV infection. This showed that the cost per HIV infection averted was $217.62 and $10.33 per DALY saved (based on Tanzanian life expectancy) or $9.45 per DALY saved if the assumptions used in the 1993 World Development Report were applied[7]. Measured against this standard, ARV treatments do not appear to be very cost-effective.

Making comparisons with other HIV/AIDS interventions is constrained by the limited evidence on their cost-effectiveness. However, it has recently been suggested that if the cost/DALY of a health intervention is less than per capita GNP, the intervention is likely to be cost-effective (Sheperd et al, 1997). Although this is not, conceptually, the way that cost-effectiveness analysis is to be used (since it should be used to reflect the relative worth of interventions *relative to each other* rather than to any absolute standard), it seems to be a useful 'rule of thumb' . Using this as a general guide, Table 8 suggests that:

- ARV prophylaxis for HIV infected pregnant women may be cost-effective in countries with a GNP/capita above US$285;
- ARV triple-combination therapy may be cost-effective in countries with per capita incomes of over US$8 000;
- prophylaxis of people exposed to HIV infection may be cost-effective in countries with a per capita GNP of over US$10 000.

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[5] The cost/DALY figures quoted in the World Development Report 1993 are also taken from the studies presented in this book.

[6] Data from the Mwanza study of improved treatment services for STIs in preventing HIV infection based on Tanzanian life expectancy

[7] These results are in line with a theoretical estimate made by Over and Piot of between $0.56 and $50 per DALY saved, depending on the various assumptions made.

2.2 Problems with applying cost-effectiveness analysis to ARV treatments

Caution is needed when using cost-effectiveness data. There are a number of difficulties with applying cost-effectiveness analysis to HIV/AIDS interventions, including ARV treatments. These need to be borne in mind when conducting cost-effectiveness studies or when using results derived from them. The major issues are discussed below.

Calculations very sensitive to drug prices

Cost-effectiveness calculations are highly sensitive to changes in ARV drug prices, which will significantly alter any cost/DALY calculation. Sensitivity analyses are therefore very important in cost-effectiveness analyses related to ARV treatments, as are re-assessments of cost-effectiveness following any reductions in drug prices.

Quantifying secondary benefits is difficult

ARV interventions may have important secondary benefits, beyond their direct impact on the individual treated or on MTCT. For example, in the case of interventions to reduce MTCT, decreased HIV transmission to infants may not be the only beneficial outcome. MTCT will lead to larger numbers of pregnant women receiving testing and counselling. Whether the result is positive or negative, this may encourage more responsible behaviour, and may also help promotion of interventions such as Vitamin A supplementation. In addition, if more people are aware of their HIV status as a result of MTCT, normalisation of HIV is more likely to occur. This should enhance prevention, which is currently hampered by denial and stigma. Knowledge of HIV status also allows PLHA early access to psychological and medical care including TB preventive therapy and cotrimoxazole prophylaxis. In the case of PEP, health workers are likely to have increased awareness of HIV infection, which may encourage safer practices in the work setting, in sexual behaviour, and in general infection control. Provision of PEP may also have important beneficial effects on staff morale (see Module 7 for further details). It is difficult to quantify any of these secondary benefits, but it is important to bear them in mind when using cost-effectiveness studies. It may be judged that these benefits justify providing some ARV treatments even when cost-effectiveness comparisons based only on primary effects are not favourable to ARV interventions.

Extrapolating from cost/DALY figures is not straightforward

It is not always easy to extrapolate cost/DALY figures to many country settings, because the studies on which they are based were generally conducted in one or only a few countries.

Effectiveness of ARV treatments is uncertain

It is difficult to estimate the effectiveness of ARV treatments for people with HIV/AIDS because the long-term impact is unknown. For some treatments, clinical trials have not been set up, are still in progress, or have yet to be designed and funded. Furthermore, effectiveness data concerning ARVs is currently limited to recent trials. This means that at this stage comparisons can only be between results of pilot research interventions and established programmes. There are often considerable differences between what can be achieved in well-resourced and managed pilot research projects, and what can be achieved in more typical operational settings.

Few cost-effectiveness studies have been undertaken and the costs included vary between studies

Few cost-effectiveness studies of ARVs have been undertaken in developing countries. Those that have been done have focused on MTCT. There is far less information about PEP and HIV/AIDS treatment[8]. In addition, cost-effectiveness calculations will vary according to what costs are included. At present there are no agreed upon guidelines concerning what costs should be included. These are needed, but in the meantime it is important to read cost-effectiveness studies carefully to identify what costs have been considered. One particular issue is whether or not the start-up costs associated with VCT services, which are needed for interventions such as MTCT, are included in cost-effectiveness analyses.

Providing coverage for "catastrophic financial risks" may be considered more important than cost-effectiveness

It can be argued that it is appropriate for governments/insurance agencies to provide coverage for "catastrophic financial risks", which the individual/household cannot afford to pay for, even if the care entailed is not cost-effective. Interventions that are not for "catastrophic risks" e.g. many treatments provided at primary care level, it could be argued, should be funded by individuals/households - even if they are far more cost-effective than interventions for "catastrophic risks". Such arguments have implications for financing policy (see section 5).

Political imperatives

Pressure on governments to "do something" may make it almost impossible to strictly apply the results of cost-effectiveness analysis in practice.

Cost-effectiveness analyses only allow comparisons within the health sector

Cost-effectiveness analysis in the health sector uses health-specific outcome measures. This means that it can be used to inform decisions about resource allocation within the health sector, but not the decisions about whether more resources should be allocated to the health sector as a whole. This issue appears to be of particular concern in Latin America, where AIDS activists have reportedly argued that governments are already funding non-cost-effective policies in other sectors, so that ARV treatments should not be competing for funds with other health programmes, but with other public budgets. This is an important argument to bear in mind when using cost-effectiveness to inform decisions

[8] one reason for this is that comprehensive strategies have not yet been formulated.

on the introduction of ARVs, or any other kind of public policy (including health) intervention.

2.3 How can the difficulties with cost-effectiveness analysis be reduced?

Box 1

- Ensure that any studies include sensitivity analyses, particularly to explore the implications of lower drug costs
- Commission studies to fill the most important information gaps
- Establish national task forces with participation from government, pressure groups, people affected by HIV/AIDS, NGOs, the private sector etc. to assist in the decision-making process
- List all possible secondary benefits and seek expert opinion about the extent to which they are likely to affect cost-effectiveness results
- Consider whether increased efficiency in other sectors, or within the health sector, could help release public resources for ARV treatments, thus providing additional resources without having a detrimental effect on either the health sector or other parts the public sector
- Consider if coverage of catastrophic financial risks is more important than cost-effectiveness
- Supplement studies with other types of economic analyses
- Consider to what extent ARV treatments fit with overall development objectives.

It may be especially helpful to supplement cost-effectiveness analyses with other types of economic assessment. A particularly useful approach is to consider the "opportunity costs" of investing in ARV treatments. This means that the question is not "Are ARV treatments cost-effective?" but *"What is given up by investing in ARV treatments?"*. If the cost of an ARV intervention can be estimated and if the costs of other types of HIV/AIDS care and prevention activities can also be estimated, it is possible to illustrate what potential benefits would be lost by investing resources in ARV treatments. For example, what prevention activities could be funded for the cost of ARV interventions? What level of counselling and testing, and treatment of opportunistic infections, could be funded for the cost of ARV treatments? The answers to such questions should both (a) inform decision-making and (b) help to provide justifications for the choices made. If such data are not already available, assessments should be undertaken.

This type of analysis could also be extended beyond HIV/AIDS prevention and care: for example, how much malaria control could be provided, how many tuberculosis cases could be treated, how many children could be immunised, with the funds required for ARV treatments? Similar questions could be asked for non-health sector activities too. How many children could be educated at primary level, what basic infrastructure could be installed or repaired, for the cost of ARV treatments? *These kinds of questions that are of importance in any particular case depend on the relevant unit of decision-making(e.g. national, provincial, district health system, particular programme etc.)*

3. Are the necessary human/physical resources available?

It is important to emphasise that *cost is not the only economic constraint to the provision of ARV treatments*. Even if ARVs are affordable, and whether or not decisions concerning their provision are influenced by cost-effectiveness studies, *successful provision in practice depends on whether the necessary human and physical resources are available and/or capable of being mobilised*. Under some circumstances, inadequate capacity - for example too few staff or insufficient laboratory services - may to be more of an obstacle to ARV treatment provision than is the securing of funding[9].

The sort of capacity which is likely to be critical is shown in Box 2 below.

Box 2: Human/physical resources required for ARV treatment

- sufficient numbers of counsellors
- counsellors trained in drug adherence counselling
- sufficient numbers of mid-wives for MTCT interventions
- laboratory services capable of offering the sometimes sophisticated tests required for monitoring of ARV treatments (see Module 5)
- extra clinic space for counselling and testing services
- adequate numbers of physicians trained in the correct usage of ARVs
- patient follow-up to ensure compliance with drugs and/or manage side-effects
- strengthened health education concerning safe feeding practices for mothers receiving treatment to prevent MTCT
- occupational health staff to implement PEP
- secure buildings for drug storage
- well-functioning drug distribution systems
- drug resistance monitoring capacity
- managerial skills to organise and supervise promotion, implementation and monitoring of interventions

A recent study in rural South Africa has estimated that there needs to be a 10-15% increase in the number of midwives, a 50% increase in laboratory staff and a 100% increase in counselling staff to implement an MTCT initiative. This is at a time when HIV-related staff sickness and premature death is on the increase and is already reducing the pool of skilled health workers. Furthermore, if the intervention is implemented simultaneously in rural and urban areas, there will not be enough trained mid-wives. *Difficulties in strengthening basic infrastructure and recruiting additional staff may seriously impede the process of introducing and implementing ARV interventions*.

Problems of capacity are likely to be *less* acute in parts of the world where health staff are in greater supply and where educational levels are relatively high - for example Latin America, the Caribbean, and parts of Asia. However, even in areas where capacity is relatively strong, the problem is still daunting given the complexities of the interventions.

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9 for example, in the World Bank's recent publication "Confronting AIDS", it is observed that "effective anti-retroviral therapy requires a highly trained, specialised physician working in a well-equipped clinic with experience performing a wide range of sophisticated tests and procedures, all of which are in critically short supply in most developing countries".

4. Equity

Equity is not an easy term to define, but is related to ideas of "fairness" and "justice". In the case of ARVs, there are two particularly important questions to ask:

- who is likely to have access to ARV treatments?
- is such access fair?

In economic terms, the issue is therefore one of the *distribution of resources* for ARV treatments. What is this distribution likely to be, and is it fair? At present, there is limited evidence concerning who is likely to have access to ARV treatments, while the question of fairness is a value judgement. Nonetheless, it is possible to suggest the following:

- access to ARV treatments will be closely connected to financing policy (see section 5). If treatments are not provided through public funding, only the highest income earners in a country, and those who are members of social security schemes which have agreed to pay for ARVs (see Box 3), will be able to obtain treatment;
- while it could be argued that access based on ability to pay is unfair, most goods and services are consumed on this basis. Furthermore, even though much health care is funded publicly, access to public services is not equal: it would need to be carefully justified why ARV treatments should be treated as a special case. If there is already unequal access to services, it is also likely that it would be hard to achieve more equal access with ARV treatments, particularly since they are likely to be relatively difficult to deliver;
- particular care is required if ARV treatments are heavily subsidised or completely funded by government. ARV treatments may then be provided to people who would have been prepared to pay for them in the private sector. If this happens, public resources will be unnecessarily diverted away from other services, which might have benefited people less able to access treatment in the private sector, including those without HIV infection. There is some evidence from Côte D'Ivoire that this situation does occur in practice (see Box 3);

Box 3: Equity and ARVs: the examples of Côte D'Ivoire and Mexico

ARV treatments are being provided in both Mexico and Côte D'Ivoire.

In Cote D'Ivoire, technical constraints mean that only a few centres have been authorised to supply treatment. This seems likely to limit access to those who live in urban centres, particularly Abidjan (the capital city). Entry criteria for pilot programmes include that patients have "the necessary financial resources and understanding of the disease and its treatment to enable them to comply with the treatment provided". This implies that members of higher income groups, who might have been prepared to pay for the drugs in the private sector, are most likely to benefit.

In Mexico, the Social Security System started to provide ARVs in mid-1997. It covers only 50% of people with AIDS. Access to services through participation in research protocols is usually limited to Mexico City and benefits small numbers of people.

Sources: Brunet-Jailly, 1998 "AIDS and Health Strategy Options: the Case of Cote D'Ivoire; Saavedra, personal communication, 1998

- since ARV treatments require specialised staff and equipment, urban populations are more likely to have access to them. Access will probably always pose problems for rural populations and some marginalised and vulnerable groups (see Module 3).

5. Financing

Decisions regarding financing policy are closely connected to issues of affordability, cost-effectiveness, and equity; and even if financing is available, it will only be successfully translated into treatment provision if the necessary human and physical resources are available. Therefore while decision-makers may regard financing as the most important issue on which they require guidance, it cannot be divorced from these other issues.

This section takes each possible financing mechanism in turn. The most important factors to consider in the context of ARVs are suggested, and the advantages and disadvantages of each option are discussed. The options considered are public funding, national insurance/social security schemes, private insurance, voluntary sector/charitable funding, community financing, out-of-pocket payment (private funding), external assistance from donor agencies, and development loans.

Box 4: Financing options and existing patterns of funding for drugs

1. Public financing
developed countries: 66% of drug costs
developing countries: usually < 20% of drug costs

2. Health insurance
includes national and private health insurance, and social security schemes
Latin America 35%, Asia 10%, Africa 8% of drug costs
great variation in whether or not drugs and HIV care are covered

3. Out-of-pocket payments
50-90% of drugs bought by households
government services increasingly charge user fees

4. Voluntary and other community/local financing
PLHA solidarity funds - especially north-south
drug donations

5. Donor financing
increasingly sectoral focused rather than disease-specific
more emphasis on prevention, limited funding of drugs

6. Development loans
increased World Bank involvement in the health sector
pharmaceutical lending
generally an interim measure

To set the discussion in context, Box 4 and Table 9 highlight key features of health financing in developing countries. They suggest that:

- public expenditure is relatively important in Latin America and Africa;

- private spending is most extensive in Asia, particularly India, but is significant everywhere;
- national insurance and social security schemes are mainly important in Latin America;
- public expenditure as a percentage of total drug expenditure is relatively low;
- most drug expenditure in developing countries is out-of-pocket expenditure;
- per capita incomes in all countries suggest that without public funding, ARVs will be difficult to afford for many people with or exposed to HIV infection; and
- external assistance is an important source of funding in only a few countries.

Such assessments will be useful in any country considering the introduction of ARV treatments, since their financing is likely to be linked to, and/or constrained by, existing financing strategies.

Table 9: Patterns of health financing in African, Latin American, Caribbean and Asian countries in 1990

Country	GNP/Capita	Public financing as % total health expendit	Private financing as % of total health expenditure	External assistance as % of total health expendi
Ghana	408	35	52	13
Uganda	188	13	53	34
Zambia	354	65	31	4
S. Africa	3 039	58	42	0
Côte D'Ivoire	609	49	48	3
Thailand	2 410	53	47	0
India	320	20	78	2
China	530	58	41	1
Bangladesh	220	25	57	18
Trinidad	3 769	62	37	1
Barbados	6 667	64	34	2
Brazil	2 970	66	34	<1
Costa Rica	2 394	74	25	1
Peru	2 108	56	42	2
Uruguay	4 656	54	46	0

5.1 Public financing

The main issues to consider in the case of public financing of ARVs are:

- what are the justifications for public, as opposed to private, funding of health care, and how do these relate to ARVs?
- would public funding of ARVs be consistent with overall health sector policies?
- can the public sector afford to provide ARVs, and if so for all or just some indications; would this be a cost-effective use of scarce public resources?
- do budget constraints and taxation policies make generation of additional public revenues for ARVs feasible?
- are the consequences of not providing any public funding acceptable?
- will public funding result in subsidised care being provided to people who would otherwise have accessed such care in the private sector?

Each of these is discussed below.

Justifications for public funding of health care in general

Public funding of health care can be justified on the following grounds:

- **externalities**: for some health conditions, there are important "externalities" - that is, the costs of that condition, or the benefits of providing treatment for it, extend beyond the individual directly affected by it. For example, immunisation benefits people other than the child immunised; tuberculosis treatment benefits people other than the person with the disease, because treatment prevents further transmission. In such instances, where private costs/benefits are exceeded by societal costs/benefits, there will be inefficiently low investment in such interventions if decisions are left up to individuals. This is because individuals are expected to make decisions based on private costs and benefits, not social ones. Therefore, public funding may be required in cases where there are important externalities, in order to ensure that an efficient level of provision occurs;
- **catastrophic risks and insurance market failure**: some health conditions are very costly to treat, and will be beyond the capacity of most individuals to finance. This means that there is a case for insurance, so that such potentially "catastrophic financial risks" can be shared (see also section 2). Furthermore, since markets in private health insurance may fail - some people may be unable to obtain insurance because they are "bad risks" or already have chronic conditions, and cost containment is difficult - a case can be made for public funding;
- **health care is a special case**: it may be judged that, unlike most goods and services, access to health care should not be based on ability and willingness to pay. Health care is a "basic right" to which everyone should have access, and the consequences of basing access to health care on ability to pay are unacceptable.

To what extent do justifications for public sector funding apply to ARVs?

The above arguments could be used to justify provision of ARVs, at least in some instances. Externalities exist in the case of MTCT and PEP, because prevention of transmission to children and infection of people exposed to HIV infection will have benefits beyond the individuals treated. HIV/AIDS is also a catastrophic financial risk - most of those affected cannot afford to purchase treatment themselves. And like other health interventions, it may be considered that access to ARVs should not be a function of ability to pay. Private financing is likely to restrict access to a high-income minority (see also section 1), and this may not be considered acceptable.

Consistency

Nonetheless, even if these arguments are accepted, it is important to be consistent. Are such arguments used for other aspects of health care provision? As Box 4 and Table 9 show, much care is not financed by the public sector: is HIV/AIDS different enough to be seen as a special case? Public provision of ARVs may also not be consistent with certain health sector reform initiatives: for example, increased emphasis on user fees, cost containment, essential health packages where cost-effective services have first call on public resources, and private sector provision (see also section 7). As Box 4 shows, public funding of drugs is low: yet with ARVs, public funding would mean that most, if not all, of the drug costs would have to be covered.

Affordability and cost-effectiveness

If ARV treatments are likely to consume a large share of health sector resources, public funding may not be practical, and if they do not appear to be very cost effective, it may be hard to justify their provision. Affordability will also be influenced by wider government priorities, such as taxation levels and public sector borrowing targets.

The consequences of not providing public funding

The consequence of not providing public funding is that access to ARVs will be limited to those who can pay for them on an individual basis i.e. those in the highest income brackets.

Access issues may arise even with public funding

Public funding does not guarantee that access will not vary according to socio-economic status or geographical area. For example, because specialised skills and sophisticated equipment are required, it may only be feasible to supply ARVs in a few locations - often capital cities and other large urban centres. And because compliance to drugs is crucial, entry criteria to treatment programmes may have to favour those with higher socio-economic status (see Box 3 for examples from Mexico and Côte d'Ivoire).

5.2 Social health insurance

Social health insurance involves insurance schemes where membership is compulsory. These can be national insurance schemes, to which everyone (or at least those in formal employment) must contribute; or social security schemes, which can be national in scope but are frequently linked to employment in a particular company or sector. Social insurance is an important source of health sector funding in Latin America, but is of minor importance at this stage in Africa and Asia (see Box 4). Therefore, social insurance has most potential to fund ARV treatments in Latin America.

One advantage of social insurance, as opposed to private health insurance, is that people cannot be excluded from cover: everyone contributes, everyone is covered. The main issues for ARVs and national insurance schemes/social security schemes are therefore:

- can schemes afford to provide cover for ARV treatments? (see section 1)
- if schemes fund ARVs, will HIV-seronegative individuals be affected by reduced access to other services?
- if existing funds are unlikely to be sufficient, can premiums (the contributions made by employers/government/individuals) be increased to provide the required funding? Will this be acceptable to those who do not require ARVs but who will be expected to pay higher premiums?
- is provision of ARV treatments/increased premiums compatible with health sector reform initiatives related to health sector financing? For example, HSR may include an emphasis on cost containment and reduced government contributions to schemes.

Conceptually these issues are identical to those faces by publicly financed systems, the only difference is the population that is covered by each. These four questions will need to be addressed in any country or institution considering the funding of ARVs through social insurance. *It is likely that in countries where HIV seroprevalence remains relatively low, where social insurance is widespread, and where incomes are comparatively high, social insurance does have significant potential to fund ARVs*. In Latin America, where these

three characteristics exist, social insurance may therefore be an important facilitator of ARV treatments. Both Costa Rica and Mexico, for example, are funding ARVs through this mechanism.

It is much less likely to have significant potential in Asia and Africa, simply because social insurance is very limited in these regions.

Where only part of the population is covered by social insurance, these programmes often exacerbate inequities in access between the insured and uninsured.

5.3 Private health insurance

Private insurance is likely to be of limited value. Companies can be expected to try to eliminate bad risks: evidence from the USA shows that some insurance companies use HIV testing to eliminate poor risks from pay pools, and cost-conscious employers have tried to exclude AIDS patients from group insurance. In South Africa, individual companies are offering lower premiums to people with low HIV/AIDS risk, and in order to remain competitive, other companies are likely to be forced to do the same. This means that HIV-infected people will find it hard, if not impossible, to obtain coverage; and it is increasingly common for policies to specifically exclude cover for HIV/AIDS-related health problems. It is worth noting that the majority of HIV/AIDS care is financed through the public sector even in the USA, where total public sector funding of health care is about 40% of total health spending. In other Industrialised countries public sector health funding is a much higher proportion of total health expenditure. It is therefore unlikely that private insurance has much potential to be a major source of funding for ARV treatments elsewhere.

An exception to the tendency of private insurance companies to exclude coverage for HIV/AIDS, however, is a company in South Africa which is offering insurance to employers rather than to individuals. This specifically covers the health care needs of HIV infected people, including provision of ARV therapy. Replication may depend on the ability of governments to put in place, and enforce, appropriate regulation on the private insurance market (see section 6).

5.4 User fees and other out-of-pocket payments

ARV treatments represent a large proportion of income at the level of the individual/household. This means that full cost-recovery through user fees for on-going treatment of people with HIV infection is unrealistic, except for a small minority of patients with much higher than average incomes. However, short-courses for PEP and MTCT may be more affordable (see section 1. for how this can be assessed), and partial cost-recovery may be possible in some settings. For example, partial cost-recovery for ARV treatments for AIDS patients is planned in Thailand. For these sorts of cost-sharing approaches to succeed, initial subsidies may be required. This is because sufficient confidence in government-run health services will have to be generated if individuals/households are to be willing to pay what may be a significant portion of disposable income for ARV treatment costs.

A potential difficulty which it is worth noting is that as partial and interrupted therapy encourages the development of resistant strains, legislation to restrict ARV provision to

specialist centres and approved prescribers is likely to be required. This will limit opportunities for out-of-pocket purchases.

5.6 Community-based financing and voluntary/charitable funding

Experience with community financing schemes indicates that their revenue potential is not large, and mobilising finance for costly medical treatment that does not benefit all members of a community presents obvious challenges. Solidarity funds with NGOs and community organisations may be a potential strategy, especially if strong PLHA North-South alliances are developed. Such relationships can mobilise drug donations, but may be relatively unstable in the long-term and only benefit small numbers of individuals. Furthermore, these initiatives often rely on highly motivated individuals, and high quality medical supervision, regulation and quality control may be difficult to ensure. Even when such schemes exist solely for supplying drugs, they are not useful or usually not sustainable, unless they have a broader purpose and are linked to the overall health system.

5.7 Donor financing and development loans

Donor financing and development loans may be a partial source of funding for the most cost-effective interventions in the near future in some low-income countries. These interventions would be for prevention of MTCT and perhaps PEP for health staff. However, convincing arguments will have to be put forward to secure significant levels of funding, and the reliability of long-term donor financing for such programmes cannot always be assured.

5.8 Public/private co-financing arrangements

Semi-private financing exists in all countries. It is often employment-based and reserved for employees and their dependants working in specific areas. It includes occupational health services and company hospitals (e.g. in the mines, banks or large agricultural concerns), and services for government employees, the police and the military. These may offer specific opportunities for government/private sector co-financing opportunities, especially for the more highly trained employees whose health and productivity is of significant value to the company.

Such opportunities need to be explored on a case-by-case basis. Care needs to be taken to avoid this becoming a mechanism for indirectly subsidising an urban elite in relatively high-status and well-paid employment.

In conclusion, while partial cost-recovery from patients may be feasible in middle and high-income countries, the public sector or social insurance schemes will have to finance the majority of ARV treatment costs. This means that *unless the public sector can afford to provide a substantial portion of the funding required for ARV therapy, or unless social insurance is widespread, it is unlikely that provision to anything but a small minority of patients is feasible*.

6. Provision

In recent years there has been increased recognition that financing and provision of health care can be treated as distinct issues. Even if public funding finances health care, this does not mean that public provision is required: for example, government can contract with NGOs and the private sector, thus funding care but not taking direct responsibility for its provision. In addition, where the public sector does not fund health care, this does not mean that it should not be involved in provision, for example through regulation of the

private sector or through setting the overall policy framework within which the health sector operates. In the area of ARV treatments, the private sector will have an important role, especially where public funding is non-existent or limited. NGOs, which have frequently been instigators in other areas of HIV/AIDS care, are also likely to be involved. In addition, the pharmaceutical industry is also of fundamental importance, since pricing policies on ARVs are arguably the single biggest influence on whether or not ARV treatments can be widely provided. This section therefore discusses, in general terms, what role each can play in provision of ARV treatments, highlighting important issues to be considered in each case. These roles are largely those of *direct provision, regulation, negotiation, facilitation and price-setting.*

Box 5: The role of different players in provision of ARVs

Private practitioners/clinics/hospitals: can play a major role in direct provision. Concerns include limited experience with use of ARVs, resulting in inappropriate prescribing practices and possibly drug resistance; exploitation of patients. Restricted to those who can afford to pay. If it functions well, it will help avoid unnecessary diversio of subsidised treatment to those who can afford to pay themselves. May need training support/guidelines.

Pharmaceutical industry: pricing policies; negotiation with governments/employers. Of fundamental importance to making ARVs widely available.

Government: direct provision; development of guidelines/overall policy framework; provision of support to other providers e.g. training programmes; negotiation with pharmaceutical companies and international organisations; regulation of the private secto accreditation schemes may be particularly useful. Key role in overall development of partnerships among all those involved in provision.

NGOs: direct provision; advocacy. May lack experience with ARVs and often not well incorporated in overall policy framework. Need to avoid duplication of other private an public services, possibly through more formal inclusion in policy development/planning. Have advantage of being seen as trustworthy.

International organisations: negotiation with pharmaceutical industry; technical suppo to government/NGOs/private sector, dissemination of lessons of experience.

6.1 The private sector

The private sector is likely to become a major player in provision of treatment for both opportunistic infections and ARV therapy. This has already occurred in the USA and, for the urban elite, in many parts of sub-Saharan Africa. Serious consideration should therefore be given to the sector, which includes private practitioners/clinics/ hospitals, the NGO sector, and semi-private health providers (company clinics).

The main concerns with the private sector are:

- few doctors have had any training or experience of using ARV treatment;
- the necessary infrastructure for proper use of ARVs and management of patients may not be available;

- exploitation of patients may occur - the profit motive rather than the welfare of the patient may be the main motivation for what treatment is provided. Desperate people living with HIV/AIDS may be prepared to pay for inappropriate or partial therapy if this is all they can afford, as there is a widespread belief that some drug is better than none and will have a worthwhile effect;
- incorrect use of ARVs may lead to drug resistance: if private sector providers use ARVs inappropriately, there is a very real danger that drug resistance will rapidly emerge.

These concerns mean that government has an important role to play in provision of training and guidelines, and in regulation (see below).

Theoretically, an advantage of collaborating with and supporting private sector providers is that those who can afford to pay for treatment may be persuaded to use them, thus 'freeing up' more public sector resources for those in more genuine need of subsidised ARV treatments. However, such 'freeing up' of resources has never been shown empirically, and the likely magnitude of any such gains would be quite small.

6.2 The pharmaceutical industry

The importance of the pharmaceutical companies who research and develop, manufacture, market and sell ARVs cannot be underestimated. Their pricing policies and willingness to develop special - perhaps unique - partnerships in the area of ARV drugs will be critical in determining what level of ARV provision is feasible. Without substantial reductions in drug prices, access to ARVs is likely to remain restricted. Some positive developments have already occurred, with the price of some drugs being substantially reduced in early 1998. Collaborative partnerships among companies, international organisations and governments may facilitate further progress.

6.3 Government/public sector

The concerns with private sector provision and drug pricing mean that government, and the public sector as a whole, have a key role in ARV treatment provision, even if the public sector is not a direct provider of care. This is particularly the case in countries where the private sector is very extensive, such as India. Partnerships with private sector providers need to be developed to facilitate both training and regulation, and constructive partnerships with pharmaceutical companies are essential.

An important way of improving the quality of private sector provision is to offer training and instruction in the best ways to use ARV treatments. Supervisory bodies such as national Medical Councils may be especially important partners in such initiatives. Moreover, the public sector has the mandate and resources to conduct regular in-service training, and the skills to supervise and assure the quality of such post-graduate education. A requirement to complete training in use of ARVs (perhaps through the award of a certificate of competence on completion of a training workshop) would ensure good standards of clinical practice, and could be used as a way of demonstrating to the public that private practitioners have attained a certain competence in the use of ARV drugs. Such accreditation schemes are particularly useful because:

- they give providers an incentive to undertake training: with accreditation, providers may be able to attract fee-paying patients away from untrained competitors, and avoid loss of existing patients to those with accreditation;

- they provide consumers with more knowledge about which providers will provide a good service.

A free or subsidised training scheme, if widely advertised and correctly administered, could therefore be used to develop a regulatory system based on those who were registered or licensed, and approved for ARV prescribing.

The use of voucher systems could also help to assure quality. If some public funding is available for ARV treatments but public provision is not considered a viable option, the government could issue vouchers which patients could only use at a range of licensed private practitioners. This would ensure that patients received quality care, and private providers would be able to redeem the vouchers in the form of cash (or perhaps drugs) at the local health service. Such services have been piloted in several different regions for a variety of non-HIV-related problems.

Government's role may be to provide the necessary in-service training and guidelines for ARV treatments, including monitoring and adherence (in whatever programmes are to be implemented); and then to supply regularly, at cost or with subsidy, a pre-fixed amount of ARV drugs for that NGO's use (some NGOs may even be able to bear some of the costs of setting up the necessary services by raising money from their overseas partners). Government may also contract with NGOs to provide defined services in their catchment areas (see below).

Maintaining the integrity of the drug supply is likely to be a key responsibility of government. The high cost of the drugs, and their probable high resale value, means that the likelihood of the development of a black market in counterfeit and high quality drugs is high. Government is the appropriate agency to develop mechanisms (e.g. laws with appropriate punishments for offences) to protect the integrity of the drug supply, and should regularly monitor and evaluate their performance (see Module 8 for further details).

Government may also have a role to play in monitoring and regulation of the private insurance market. This is particularly the case where innovative schemes are being developed, since this will facilitate an early response to problems which arise, allow important lessons to be learned, and enable public awareness of the advantages and pitfalls of these initiatives to be raised.

Government is the appropriate body to negotiate with pharmaceutical companies, and to facilitate the development of constructive partnerships with them. Much can be achieved in this way, as the drug reductions negotiated by the Uruguayan government shown in section 1 illustrate.

6.4 NGOs

NGOs are significant health care providers in many low and middle income countries and have a number of strengths. They often have important financial links with sponsors and charitable partners in industrialised countries, and donors frequently channel considerable budgets through NGOs because of their good reputation for financial probity. Some NGOs and CBOs may have also have links with PLHA networks in industrialised countries, and be capable of accessing additional ARV supplies and perhaps specific technical support and training for their optimal use. Moreover, NGO services are usually

run independently from any government services and there is little need for management and supervision.

These strengths may imply that NGOs have an important role to play in ARV treatment provision. However, some caution is needed. The sustainability of NGO provision of ARV treatments in the medium and long-term is uncertain: NGOs are often not self-supporting and receive explicit subsidies from governments and/or staff secondments, which may be withdrawn. Links with PLHA networks also depend on many factors beyond the control of individuals working for the NGO, so they may not be reliable in the long-term. In addition, NGOs may have an ambiguous relationship with government health services. They may be poorly regulated and there may be a need for NGO providers to be brought within the overall policy framework of the publicly managed health service to ensure that a parallel service, or a service catering for a minority population, is not given preferential funding.

NGOs will require training and guidelines on ARV treatments from government (see above), and may be suitable contracting partners for government. For example, the government could fund an NGO to provide a defined ARV service in their catchment area. However, NGOs are still likely to require support for specific capital items such as the building of secure new dispensaries and storage facilities for high-value ARV drugs.

The role and place of NGOs and CBOs in specialist therapeutic care such as provision of ARV treatments, where specialist expertise is required, is an issue which needs to be examined further.

6.5 International organisations

International organisations are unlikely to become involved in extensive direct provision of ARVs. Their major role in provision is likely to be in helping to facilitate and negotiate constructive partnerships between governments and pharmaceutical companies, in dissemination of lessons of experience from a wide variety of countries, and in provision of technical assistance.

7. ARVs, economics, and health sector reforms

Many governments have been in the process of reform of their health sectors since the mid-late 1980s. This section therefore briefly discusses the main reform initiatives that have been observed, many of which have an economic aspect to them, and suggests their implications for the introduction of ARV treatments into health systems. The common reform themes include:

- decentralisation of decision-making to district health systems;
- essential health care packages, in which the most cost-effective interventions have first call on public sector resources, are emphasised;
- clear separation of the bodies who have responsibility for financing and provision of care;
- cost control linked to both insurance and user fees;
- increased role for non-taxation based financing mechanisms such as insurance schemes and user fees, with reform of insurance in particular linked to the need for effective cost control;
- a focus on performance-based accountability, to replace top-down administration;

- promotion of the role of the private sector and the importance of collaborative partnerships between the private and public sectors; and
- greater prominence for issues of equity and quality.

Wherever decentralisation of decision-making to district level (particularly of decisions related to budget allocation) is occurring , the issues discussed in sections 1 to 6 of this module will need to be considered at district as well as national level - national level remaining relevant because even with such decentralisation, the MoH is usually still responsible for setting the overall policy framework within which the entire sector operates. It is therefore important that managers at district level are provided with information (for example this module) which will assist them to make the decisions for which they are now being made responsible. This is particularly necessary given the emphasis on essential health packages, in which cost effective interventions are supposed to have first call on public resources. Wherever district managers are to be responsible for decisions regarding whether or not to fund ARVs from their budgets, it is critical that district health teams be provided with information (and possibly training) concerning evidence on cost effectiveness, how to assess cost effectiveness, the problems that exist with cost effectiveness analyses, and how difficulties with cost effectiveness analysis can be minimised. Section 2 of this module is therefore very relevant in the context of HSR. Section 3 is also relevant, because decentralisation of decision-making should provide managers with greater autonomy in how they can allocate and mobilise resources. Indeed, decentralisation of such decisions may be necessary if the resources required for ARV treatments are to be put in place in a timely way, since decentralisation should provide more flexibility in deployment of resources and facilitate more rapid decision-making related to recruitment/purchase of new inputs.

The main implication of the separation of the financing and provision functions in the health sector for ARV treatment is the increased potential for the private sector to play a role in provision, even when public funds are used to provide the necessary finance. This also ties in with the general emphasis on promotion of public/private partnerships in HSR, and suggests that the discussion of the role of different players in provision of ARVs in section 6. is of especial relevance. In addition, the focus on quality assurance in HSR indicates a key role for the public sector in regulation and monitoring of ARV provision in both the public and private sectors - again discussed in section 6.

The emphasis on non-taxation based financing mechanisms in HSR means that the discussion of financing options in section 5 needs to be read with that overall context in mind. This section suggested that user fees and private insurance are unlikely to be viable financing options for ARVs, and that the most promising options if provision is to extend beyond a small minority are public funding and social insurance. Yet HSR tends to play down the role of public funding, and to emphasise cost containment (and sometimes extension of coverage, as in Colombia) within insurance schemes. Limits on public funding, and cost containment in insurance schemes, make ARV financing through increased funding from these sources less likely. Instead, diversion of resources from other services, or improvements in efficiency in other areas of health care delivery, are likely to be the main ways in which insurance schemes fund ARVs. This has equity implications, since in the absence of improved efficiency and increased resources, HIV sero-negative people are likely to be penalised. Certain aspects of HSR therefore have potential to be in conflict with some of the options for financing ARVs.

Module 3

ARV Treatments: planning and integration into health services

The following module provides guidance for planners, managers and HIV care providers in resource constraints settings who may be introducing antiretroviral (ARV) treatments in their services or in situations where ARV treatments are currently available, such as the private sector.

Before setting up ARV services key planning questions need to be addressed. A framework for these questions is provided in Table 1, which summarise decision options. The organisation of interventions with ARV treatments is discussed in section II, quality management in III, access to ARV treatment in IV, and the creation of information systems is discussed in section V. Section VI addresses the need for partnerships to ensure sustainability and section VII focuses on monitoring and reporting.

I. Introduction

The incorporation of ARVs into existing heath care services, in a safe and effective manner, is challenging; as is securing sustainable financing of such interventions.

Key issues to be addressed before introducing ARV treatment into existing health systems include: establishing laboratory capacity, as well as mechanisms to control drug supply; assuring quality management; informing the public about the benefits and implications of ARV interventions; providing training and assuring an adequate number of health care and support staff.

Characteristics, specific to ARV interventions, require that these issues be resolved promptly:

- ARV drugs are particularly high-value items; therefore, regulatory mechanisms must be secured to avoid misuse or misappropriation.
- ARV treatments are complex to use and monitor.
- ARVs can easily be inappropriately prescribed or misused with little health gain and potentially adverse public health consequences, such as the development of drug resistance.
- Interruption of the drug supply may have serious repercussions for patient care and overall programme efficiency.
- Additional staff time and technical training is required for patient counselling on adherence to the complex tablet regimens.

When introducing ARV treatments into health care services the following approaches may be adopted:

1. Attach a new ARV treatment service, specially organised as a parallel or vertical programme, to private or public health services.
2. Develop a phased approach where existing health care services for people with HIV are adapted and strengthened to incorporate ARV treatments.
3. Integrate ARV treatments into general health services by training existing staff and modifying the current infrastructure for ARV intervention.

Decisions on the implementation of ARV interventions are dependent upon the local and regional context. Critical factors to consider include:

- Seroprevalence of HIV in the country/community
- Attitudes toward HIV in the country/community
- Existing health system and support services
- Commitment to ARV interventions
- Maturity of the epidemic and stages of development of associated support services
- Financing options

Effectively initiating ARV interventions require general health care system strengthening. However, specific programmes, such as the implementation of mother-to-child transmission of HIV (MTCT) prevention in antenatal care and maternity services, and providing antiretrovirals for post exposure prophylaxis (PEP) of health care staff may also need to be considered.

The decision to expand pilot initiatives to national programmes should only be taken following a careful analysis of the requirements for the

intervention and an evaluation of pilot programmes on the clinical, operational and social effects. Sections of health service infrastructure may need to be improved before a larger scale intervention can begin. Assumptions made in the pilot phase with regard to support services will need to be analysed to ensure project feasibility.

Table 1: Questions options and criteria for decision making when considering planning an ARV intervention

Question	Options	Criteria for decision making
1. Is financing secure?	• Delay implementation if financing for sustained use is not guaranteed • Proceed if interim budget is sufficient for initial or pilot implementation phase(s) • Proceed if finances are secured	• Sustained reliable govt and external funding • Audit • Accountability • Requirements for funding • Requirements for renewal of budget • Potential cost recovery
2. What methods of distribution and procurement will be used?	• Vertically developed and managed • Integrated within existing drug distribution form public or private sector • Phased approach	• Management capacity • Quality assurance • Financial control • Access • Efficiency in use of resources • Distribution system which can respond rapidly
3. How will the intervention be introduced and where will it be based?	• Introduced as a pilot study • Services linked with existing public/NGO AIDS care centre • Delivered in approved specialist centres exclusively • Delivered in private sector	• Location of pilot sites • Location of service delivery sites • Geographic accessibility • Financial equity • Distribution issues
4. How will the quality of the intervention be monitored?	• In depth quality assurance strategy • Medical audit	• Staff and patient involvement • Sustainability of monitoring • Monitoring time-scale • Define process indicators
5. Who are the important partners in ARV management?	• PLHA support groups • Community based organisations • NGOs • Private sector • "Donor" community	• Information process • Counselling services • Patient adherence • Provision of services • Regulate existing use of ARVs

I. **Organisation of ARV Treatments into HIV Care and General Health Services**

Methods of incorporating ARV interventions into existing HIV care services need to be determined before project onset. Questions regarding the implementation of ARV interventions need to be answered such as:

- Should the management of drugs, project monitoring, and follow up be created as a separate vertically organised and funded service or integrated within existing services?
- How will HIV/AIDS clinical care fit in with a district health service that is in the process of decentralisation or currently decentralised?

Integrating ARV treatments with other services

The method for introducing ARV into existing health services is dependent upon local resources. Although integration is likely to be the final goal, initially, vertical approaches may be more feasible. A national authoritative committee to guide ARV implementation should be established to serve as the key mechanism for achieving consensus on programme initiation.

Experience from other interventions and programmes, which initially began vertically, but are now being integrated in the general health services, may provide insight into effective programme implementation and management.

Management at the national level

The national committee should be specifically organised to guide ARV interventions. This may be either a new committee with sole responsibility for the ARV intervention and other HIV drugs, or an existing drug regulatory body. A multidisciplinary approach is best, and maintaining links with key partners including "care focal points" from HIV/AIDS programmes, experts (pharmacists, physicians, nurses and counsellors), consumer organisations (PLHA support groups) and drug control officers (pharmacists, administrators, private sector representatives) is critical. Progress of the ARV initiatives will ultimately depend on how well this central body performs its duties.

The tasks of the national committee should include the introduction, phasing, implementation and evaluation of this intervention, as well as the following:

- Arrangement of financing for the intervention, be it from public and/or private sources.
- Establishment of a regular distribution system for ARV drugs.
- Identification of sites for ARV interventions.
- Development of process indicators and evaluation tools.
- Provision or dissemination of public information on the advantages and implications of ARV treatments.

-

To generate broad consensus, immediate tasks for a national committee include:

1. National policy formulation on ARV, including financing, pricing mechanisms and phasing.
2. Development of country specific practical guidelines.
3. Capacity building for clinicians, counsellors and drug administrators at identified sites.
4. Estimation or assessment of realistic drug needs.
5. Strengthening and development of a storage and distribution system; ensuring regularity of supplies and distribution.
6. Selection of clinics/sites suitable for the provision of ARV treatment.

Organisational options for start up at site level

Most countries affected by the epidemic provide HIV/AIDS care in a variety of settings, such as:

- Special units in major hospitals (district, mission, provincial and national referral institutions) where HIV/AIDS clinical care is often linked to an NGO to assure comprehensive care needs (Patient Support Units and HIV clinics).
- Private physicians' clinics.
- Clinics within the workplace.

The decision as to which site should initiate ARV interventions should be based on site fulfilment of the minimal requirement standard, as described in Table 2.

It is best to first pilot the ARV intervention at one or a few sites meeting the eligibility criteria, and monitor the programme for information regarding effective ways of integrating ARV treatment into existing HIV care before expanding the initiative.

Limiting the intervention to sites that meet the minimum requirements will likely raise questions of equity and accessibility. Some physicians may complain that their professional integrity is being questioned if they cannot freely prescribe. Therefore, it is critical that the national committee develops a communication strategy with professionals to inform them of the reasons for selecting their approach, and include the private sector in programme initiation discussions.

Table 2: Implementation steps to consider for ARV program introduction

Steps	Actions to be considered
• Design ARV implementation • Identify sites for pilot implementation	• Set up national committee • Identify staff for ARV provision • Build on existing HIV care provision • Recruit new staff as necessary • Provide in-service training for staff
• Consider infrastructure viability for additional clinic requirements	• Estimate patient population • Allocate necessary clinic space • Rehabilitate existing premises
• Review current VCT services and follow up counselling and care support	• Identify access and quality of existing VCT services • Plan for follow-up counselling to ensure drug adherence • Recruit and train staff as necessary • Expand premises as necessary
• Plan linkages between ARV treatment and other clinic services such as family planning, TB, STI, home care, antenatal care, and general medicine	• Identify services related to ARV interventions • Develop referral guidelines • Train staff on ARV interventions
• Set up necessary laboratory services for ARV intervention (see module 5)	• Employ/train staff as necessary • Determine equipment needs, order, install and maintain • Build/rehabilitate laboratory premises as required • Set up supply system • Organise quality control system
• Establish or strengthen systems for drug clearance, stock control, drug storage, distributing and monitoring ARV use (see module 8)	• Employ and train staff as necessary • Determine and attain equipment for safe drug storage • Develop an audit/accounting system • Build/rehabilitate pharmacy premises as necessary

Organisational Requirements:

1. **Training and support of health care staff**

   Training in ARV interventions is a prerequisite for staff at the unit where ARV will be implemented. Moreover, information sharing about ARVs must be made available to a wide cross-section of clinic staff. Continued training and updating of correct information/knowledge of health care workers should also be built into the system.

   Health care staff undertaking new duties as a result of the ARV intervention may feel overworked and possibly suffer "burnout". Support for health care staff should be planned to minimise staff stress.

2. **Motivation and time**

A positive work environment is important in maintaining staff morale and commitment. Extra time should be allocated for staff to adequately explain to patients:

- Complex drug taking schedules, timing, and practice.
- Monitoring the effectiveness of ARV therapy, adverse effects and drug interactions.
- Counselling those who do not respond positively to therapy.
- Updating on new drug developments.

Staff who can effectively interact with and assist patients, their needs and reactions, and provide complex drug counselling should be recruited and supported.

1. **Space**

   All programmes will require that suitable space be arranged for intensive drug counselling. Rooms where confidential sessions can be held and where local PLHA support groups can meet to provide peer support should be arranged. Space requirements for confidential counselling can be significant be should not be underestimated.

2. **Laboratory support**

In limited-resource settings, relatively inexpensive, simple methods for CD4 counts and standard methods for HIV diagnosis, as well as monitoring of ARV side effects, and diagnosis of opportunistic infections will require additional supplies, staff and space. This may be organised with the support of one central laboratory responsible for quality control and training. Where possible, facilities for monitoring ARV treatment response should include measurement of viral load. However, this may not be available in many developing countries. Laboratory requirements are discussed in detail in module 5.

From vertical to horizontal service delivery

ARV interventions initiated at specialised centres should be monitored, and if successful, included as part of an integrated follow-up service at peripheral clinics or primary health centres where adherence can be reinforced and other care and support requirements can be met. This continuum of care for patients receiving ARVs, as well as cross-referral between hospitals and the community is critical and will require extensive collaboration between clinic staff and care providers in the community.

Boundaries between services are often difficult to define. For example, questions concerning limiting the role of counsellors to ARV-MTCT programmes (VCT, ARV follow up, infant feeding and family planning options) or incorporating counselling services for entire health facilities are often debated. Decisions regarding the role of counsellors should be determined in the local context. However, different solutions maybe adopted at varying stages in the implementation process.

For ARV interventions to be safe and effective, they must be well resourced and staffed. Tensions between services in the same facility may result as disparities with other clinical services. Pressure to utilise ARV facilities for other equally compelling clinical problems may result.

This type of operational difficulty has been witnessed with STI treatment kits, where broad-spectrum antibiotics are not otherwise available, but urgently required and administered to particularly sick patients.

I. Quality Management

Quality management and quality assurance are monitoring mechanisms used to ensure that minimal standards are met for the components of ARV interventions, including the inputs required for the intervention, the process of implementing the intervention, staff performance, job satisfaction and outcomes. The use of indicators for these various components is essential and must be incorporated into all ARV interventions or programmes from their initiation.

After the preconditions for the safe and effective use of ARV are met (see module 4), decisions regarding the implementation of the ARV intervention will be based on the assumption that a certain level of efficiency and efficacy will be delivered by the service. Staff performance, drug supply and clinical practical guidelines should all include quality control. The quality of the ARV service provided must be maintained and regularly reviewed to ensure that expected outputs are being delivered. Otherwise, failure to maintain efficient and effective services may jeopardise the future of ARV interventions.

Standards setting and the monitoring of quality and performance for drug counselling services may be a new process in many settings. Simple process indicators can be easily set up for this purpose, including items such as:

- The number of patients recollecting drug dosage schemes
- Pill collection from the pharmacy
- The length and type of each counselling session
- The number of patients who returned to discuss drug related issues
- The number of patients able to involve a "significant other" or a family member in treatment issues

Clinical monitoring is similarly carried out by reviewing process indicators such as:

- Number of patients attended
- Number of patients found eligible for the intervention
- Number of patients accepting intervention
- Number of patients with reduced incidences of:

HIV-associated morbidity

opportunistic infections

hospital admissions

- Number of patients with adverse reactions
- Number of patients with drug interactions
- Patient mortality

Monitoring adherence is critical as problems of drug resistance may result if adherence is inadequate. Adherence may be monitored through semi-structured or qualitative interviewing of patients or "significant others" to explore difficulties in adherence of drug, or laboratory surveillance of drug resistance in the community.

Feedback from the results of the monitoring processes should be provided to health care staff, thus allowing early detection and rectification of problems in service provision. Staff discussions should be encouraged to address issues which may improve motivation and performance.

Quality assurance from the patient or "user" perspective is complex to define, assess and monitor. Interviewing patients as they exit the service may be subject to bias, although important breakdowns in the quality of the service can be quickly identified in this manner. More sophisticated methods of determining patient satisfaction include focus group discussions and household surveys. Although these are difficult and timely to conduct, they may provide critical process information. Partnerships with PLHA support groups or community-based organisations may prove helpful in assessing the quality of ARV services delivered, as perceived by the patient.

I. Access to ARV Treatment

Technical complexity and costs of ARV therapy make it likely that ARV programmes will be piloted before widespread implementation occurs. Often, the intervention will be introduced in a limited number of facilities with the capacity to deliver an effective service. However, it must be noted that in many settings, the prospect of offering universal coverage with ARV programmes is remote, even if the goal is to reduce MTCT.

The issue of who will benefit from "limited access programmes" may result in serious operational problems in ARV programme implementation. In many countries, access will be limited to those who can afford to pay for drugs, even if subsidised, or to those who live close to specialist centres or district referral points. A few middle-income countries such as Brazil, ensure universal access and free ARVs as a legal right, but in doing so face managerial, quality assurance and sustainability challenges.

An effective referral system, with set criteria for eligibility, will be required at the introduction of ARV treatments. These criteria will have to consider issues of equity in determining access. Deciding who will partake in designing these criteria, as well as making information about the services widely available, is central to ensuring that the referral system operates effectively.

Equity in the provision of ARV treatments

The potential for ARV treatment services to be highly inequitable exists, particularly in high-prevalence countries with limited resources. In certain low-prevalence, middle-income countries, those in need may be able to access ARV treatment for all indications. Nonetheless, the rationing or subsidising of ARV treatment will need to be considered to avoid that the sole criteria for treatment access become financial.

Issues concerning equity of access to treatment and care for PLHA will differ for geographic regions and social groups. ARV provision within the public health system is likely to be centralised in cities, as this is where capacity is most likely to exist within the health system to implement quality ARV interventions. This places those patients from the periphery or from rural areas in a disadvantaged position. Referral arrangements for supporting patients from other areas will entail high familial costs, such as transport, loss of income, and accommodation.

Uptake will increase if services are more accessible, but if capacity and finances are limited, services may then be overloaded. Demand may exceed supply when ARV services are introduced and the initial need may often be to ration access rather than to broaden it, with the issues of distributive justice being important (see module 9). This will focus the ARV programme on the need to design "eligibility criteria", including clinical, psychological, economic and support criteria.

Guidelines for eligibility

National authorities must determine ways of obtaining broad consensus on ARV treatment interventions. Guidelines for eligibility will have to be drafted by national authorities based on these broad public consultations. Transparency in establishing criteria for entry into the ARV intervention programme is critical. These guidelines should also be made public and widely disseminated.

Guideline recommendations should be country and context specific, decided upon only after considerable debate. The debate itself, as a consultation exercise, is an important part of the ARV introduction process. It should be steered by the national committee guiding the ARV intervention programme, and will require that broad political support be obtained. It should be noted that this might prove to be a very time consuming process, therefore, this should be factored into the timetable of programme introduction.

Once these "guidelines for eligibility" have been determined, the process of implementation needs to be clearly delineated. Consistent monitoring of the intervention will be required.

V. Information Systems

There will be great public interest, expectation and confusion about any ARV programme as it is being planned. Many misunderstandings may result at the onset concerning ARV treatment. For example, it is often not understood that ARV does not cure HIV. It is critical that accurate and accessible information be regularly and widely disseminated about ARV interventions to ensure public knowledge. Messages should also be consistent with information provided from other HIV/AIDS activities.

Service provision and access

Clear and simple messages about ARV interventions must be prepared and widely disseminated once a final decision regarding ARV interventions has been determined. Public information campaigns should be released prior to programme implementation. A budget should be allocated for this purpose. The information should address:

- Who will be eligible for the interventions
- How ARV interventions may be accessed
- Advantages and disadvantages of ARVs
- ARV interactions with other common treatments
- Realistic expectations of ARV therapy (emphasising that ARV treatments are not curative)
- Specific services provided the benefits of:

Reducing the number of infants infected with HIV born to seropositive mothers

Protecting staff from accidents that may transmit HIV

Certain countries have established HIV treatment information services via the Internet. Information can continually be updated as new treatments and new drug interactions become know adverse effects are discovered. Pharmaceutical companies may collaborate in this endeavour, although monitoring to prevent bias will be necessary.

It may also be important to inform the public about the costs and financing of ARV programmes. This may result in considerable debate about fund allocation. Nonetheless, this process should be encouraged particularly where large public subsidising has occurred.

Information regarding the involvement of partners should be shared with the public. In situations where the private sector is collaborating with ARV programmes, information on which private practitioners have been licensed to implement the intervention, as well as which NGOs have been sub-contracted should be disseminated to the public.

Regardless of whether ARVs are available through the public health service or not, accurate information must be provided to the public in order to avoid misuse and/or misunderstanding of ARVs.

Prevention messages: integration and reinforcement

The need to inform the public about ARV treatment and related care services affords the opportunity to reinforce HIV awareness and HIV preventive messages. Prevention messages must be widely and repeatedly stated to guard against the idea that one can be less careful. Safer sex practices should continue to be used by those on ARVs and widely promoted.

VI. Partnerships for providing ARV services

The advantages of collaboration between various care providers at the institutional level (counsellors, physicians, social workers and nurses), welfare and community based organisations, social and spiritual services, and support groups has been witnessed in the provision of care for PLHA. Examples of successful continuum of care initiatives exist in several sub-Saharan African countries and Thailand. The introduction of ARVs allows for the opportunity to build on existing networks as well as expand or initiate comprehensive support services. Methods for collaborating with the private sector and NGOs have been discussed in module 2.

Table 6: Partners in ARV interventions

Partners	Roles
PLHA support groups	• Disseminate information • Develop support and counselling services • Maintain drug adherence
Community based organisations	• Disseminate information • Social, emotional, spiritual support • Home care
NGOs	• Disseminate information • Counselling and clinical support
Private sector	• Disseminate information • Regulate existing use of ARV & referrals
Pharmacies	• Correct information provision • Follow up dispensing and early referrals

PLHA support groups

PLHA groups can be involved in the introduction of ARV treatments in a variety of ways. Furthermore, experience from several countries have shown that prevention and care is enhanced by including input from PLHA. Several ARV planning steps could benefit from input from PLHA groups including:

- Representation in the formation of the national committee guiding ARV interventions
- Guidelines for eligibility criteria
- Advocacy to increase access to ARVs
- Peer advocates for prevention and general HIV care
- Peer counselling and support to improve adherence to ARVs
- Evaluation of patient assessment of service quality

Community based organisations (CBO) and NGO

Many CBOs are active in HIV prevention and care. Moreover, /AIDS field, and a significant number have a particular focus on the care and support of PLHA people living with the disease. Like PLHA support groups,tThese CBOs play an very important advocacy role on behalf of their clients and patients. Therefore, they will need to be represented in the national debate on eligibility and entry.

; and hopefully will have some firm and robust ideas to promote.

CBOs often focus on counselling and social support services that can be attached to HIV care units in institutions such as "Patient Support Units" to ensure comprehensive care and necessary linkages with community structures and homes to ensure continuum care.

Community focus of these organisations is extremely beneficial asstrenghts they can provide realistic information about ARV sinterventions and ensure that a clear understanding of what is involved in the intervention: how to access it; what the programme involves; the likely benefits; and, possible problems that may exist, and so on. Counselling provided by CBOs may also have the benefit of strengtheningmonitoring adherence to ARV drug regimens. , a very important possible problem in many countries where compliance for something like tuberculosis chemotherapy is often very low. However because relatively few have significant clinical capacity they are unlikely to be able to assist in ARV distribution.

CBOs may be able to help in reducing certain access barriers and, thus, minimising the inequity of most programmes for those living in rural areas or in the periphery of large cities, a long way away from ARV treatment centres. CBOs may also be able to provide transport services to individuals to access the ARV intervention programmes.

either through providing bus-fares or even by making available local accomodation. This sort of initiative needs to be discussed because a successful project to increase access may end up recruiting too many patients and clients for the ARV intervention to cope with.

CBOs and religious groups often provide emotional and social support for PLHA and their families. close to home. If As ARVs are not a cure for HIV, services must include comprehensive treatment of opportunistic and associated infections. If ARV interventions are not adhered to, or are not effective, palliative and supportive care will be particularly necessary. Establishing links between CBOs and ARV services is critical for ensuring that PLHA are provided a continuum of care should treatment be unsuccessful. Often, CBOs also involved in TB care (, the DOTS approach) and care for other chronic illnesses; therefore, there is great potential that HIV/AIDS may begin to be or can be de-stigmatised at the community level.

The private for profit sector

In many countries of both the developing and industrialised world, the private sector will play an increasingly important role in promoting and prescribing ARVs. An important The main initial issue in issue in developing a partnership between the national ARV initiative andwith the private sector will probably be to regulate the existing use and delivery of ARV drugstreatments. ARVs are often widely available through legitimate sources and/or donations from abroad. It is important to develop a partnership between the national ARV initiative and the private sector to regulate the existing use and delivery of ARV drugs to avoid inadequate prescription and/or patient care., and some form of could beis thought to be a

widespread practice now in many resource-poor countries One worry is exploitation of poorly informed patients; the other is limited value for money - and the ever present spectre of poor use leading to high drug resistance rates.

Regulation and licencing can be promoted by having the government services running a series of training workshops (free or at subsidised rates) after which a certificate of training is issued. These could then be used by the private practitioner to show to the public his/her competence as opposed to competitors down the road wh did not have the certificate. Voucher schemes are also a possibility. The need is somehow to control or at least regulate the private market for ARVs to limit improper use and exploitation.

Partnerships rather than sanctions will be more likely to work.

There is a possibility of organising an extensive network of private practitioners across most countries for the delivery of ARV therapies. This model has already been implemented in some middle income countries. However this seems a limited option at least initially in many countries. Although maMnyost private practitioners maywill not have access to the necessary counselling, monitoring and laboratory facilities needed rigorously to supervise ARV treatment To set them up has considerable cost implications and this may generate significant duplication of equipment and resources., strengthening links with hospitals where counselling and laboratory services could complement the private practice may be feasible.

There are several advantages of usingHowever i the private sector in the delivery of do quality-controlled ARV services, then, particularly if the public sector health service capacity itself is somewhat limited. Several possible ways can be envisaged whereby private firms or companies contract a private health care worker to provide ARV services with drug procurement from the public sector at an agreed price.

Caution is needed in some partnerships with the private for profit sector. It is of great importance that all those who can afford private ARV treatment (usually out of the pocket rather than any insurance programme) end up paying for it and liberating the subsidised space in the government services for those most in need. Or that those organisations who can afford to pay for their employees to receive treatment contribute fully to the drug and treatment costs.

T

The private not for profit NGO clinical services

In many countries a significant proportion of the population have access to, and use, NGO-managed clinical services. It therefore is obvious that iIf ARVs are to be scaled up in implementation beyond just a few specialist clinics in the capital city, then NGO-run/supported hospitals maywill be important sites in which to incorporate an expanded programme. With financial and technicaloverseas support from various sourcesand links, these NGO-run hospitals (including "mission hospitals") often have better infrastructureinfrasutucture, drug supplies and even resources than their government equivalent; and can be relied upon to provide relatively good-quality service. It is assumed that aAudit processes are becoming standard practice in NGO services; therefore,and the expected quality assuranceand audit components may also needs to be carried out.

The advantages of this are similar to any partnership with the private for profit sector. Government need not to be involved in the day-to-day management and supervision of such an intervention ; and can take advantage of the extensive NGO clinical capacity. Indeed f In terms of increasing access and equity, incorporating NGOs is vital as they may be the sole provider of services in a particular locality.

VII. Monitoring andMonitoring and reporting

7. evaluation of the intervention

1. Data collection

Given the cost and complexity of any ARV intervention, and the often marginal(likely) tight cost-benefit and cost-effectiveness profiles, it is important that services are provided as effectively and efficiently as possible. SFrom the outsetpecial attention must needs be given to the monitoring and evaluation process, and. Important considerations include:

- in particular what data needs regularly to be collected
- ; what system of reporting and sending data to a central surveillancesurveillence/monitoring unit will be utilised
- ; how will data be analysed;
- and
- what use will be made of the summary results
- .

- Routine methods for collecting monitoring data shouldregularly must be established and properly implemented. A standard report form for , usable by all centres delivering the ARV intervention shouldshould be designed and piloted. This can then be modified for more wide-spread use., and then scaled up for general use. Pro-formas should be used in different settings and clinics for comprehensive evaluation. Staff will likely require ust have been properly trained and prepared training for the regular auditauditing purposes. Evaluation and audit need require active promotion promotion and ownership with staff, as the staff may initially find the process threatening.

and intimidating.

clinical efficacy as defined by outcome (eg reduction in vertical transmission; improvement in surrogate disease markers like viral load and CD4 count; etc)

amount of drug supplied and prescribed

integrity of drug supply

rates of HIV drug resistance (where appropriate)

behavioural aspects, especially HIV prevention activities

in-service training and refresher courses provided

specific problems which have arisen and affected service delivery (eg lack of drugs, problems in the laboratory; personnell issues)

Routine wWays to collect such data regularly must be set up and properly implemented. A standard report form, usable by all centres delivering the ARV intervention, should be designed and piloted, and then scaled up for general use. Pro-formasThe same forms should be used in different settings and clinics for comprehensive evaluation. Staff must have been properly trained and prepared for the regular audit, otherwise this task will be poorly carried out - and thus lose much of its impact. Evaluation and audit It may be important torequire active promotion ewith the value of audit and evaluation as some staff as they may initially find the process threatening and intimidating.

2. Rreporting to a central unit

Once collected, MMMMMM Monitoring data need regularly to be sent to a central unit which will process and analyse the information. It is probably best if dData should be are routinely reported every few months to the central unit. A clear chain must be set up, and when reports do not appear, a tracking device and default procedure organisedin play to ensure that the problem can be identified, the data collected, and steps taken to rectify the difficulties immediately implemented. It is best if p

, so they can be held accountable for delays and lack of data - or be rewarded for regular and efficient performance.

Such aThe central unit may best be located at the national level, perhaps within the Ministry of Health. This to some extent However, this decision depends on whether a vertically or horizontally managed service is implemented. Although, even within a decentralised health service managed at the district level, a necessary role for central monitoring remains, particularly because of the cost and central purchasing and supply of ARVs.

Table 7: Data for monitoring ARV interventions

The necessary data for monitoring and service audit
• Economic and pharmaco-economic
Amount of drug supplied and prescribed Integrity of drug supply
• Logistic
Number of patients undergoing voluntary counselling and testing Number of patients referred and counselled for ARV interventions In-service training and refresher courses provided Specific problems affecting service delivery
• Clinical
Side-effects of treatments Laboratory quality control results Clinical efficacy as defined by outcome
• Epidemiological
Rates of HIV drug resistance Proportion of patients who are HIV-seropositive
• Social and behavioural
Numbers entering and remaining in the programme Adherence/compliance to specified ARV treatment regimen Impact of psycho-social support Behavioural aspects, particularly HIV prevention activities

- Summary of information from quality assurance and/or medical audit

3. Acting on the data received

The final step in monitoring and evaluation is the use to which the data, analyses and results are put to. It is not enough just to collect the information, however efficiently this is done. TheThe data must be regularly processed and analysed. It may be best if a particular officer is identified for this responsibility. for the speed and accuracy with which such analysis is carried out and the appropriate evaluation and monitoring results are generated.

After this regular Regular review needs to be carried out of both the aggregated national and the local results. Regular audit should identify any problems with the integrity of drug supply. Cost-effectiveness and cost-benefit data could also regularly be generatedgererated if economic analysis and review is available.

Problems identified by "front-line" staffFrom the point of view of the staff at the local care facility, must be attended in the "front-line" as it were, it is very important that any problems identified - or generally recognised and reported upwards for some sort of action - toare actuall speedily and effectivelyy dealt with in a speedy fashion, otherwise. If not confidence in the system will deteriorate, and possible negative repercussions may include minimal effort being exerted into collecting the data, in the first place, further undermining the process.

WHO/ASD/98.1
UNAIDS/98.7
Distr: General

Guidance Modules on Antiretroviral Treatments

Module 4
Safe and Effective Use of Antiretrovirals

Joint United Nations Programme on HIV/AIDS (UNAIDS)

World Health Organizationon (WHO)

WHO/ASD/98.1
UNAIDS/98.7

Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Robert Colebunders, Institute of Tropical Medicine, Antwerp, Belgium for preparing the text of this module;

Dr David Cooper, University of South Wales, Sydney, Australia, Dr Danielle Mercey, University College London Medical School, London, UK, Dr Mary Ann De Groote, University of Colorado, Denver, Colorado, USA, Dr Kevin De Cock, Centers for Disease Control and Prevention, Atlanta, USA, Professeur Jean-Pierre Coulaud, Hôpital Bichat-Claude Bernard, Paris, France, Dr Badara Samb, Institut de Médecine et Epidémiologie, Hôpital Claude Bernard, Abidjan, Côte d'Ivoire, Dr Mary Couper, Division of Drug Management and Policies, WHO, and Dr Pedro Cahn, Fernandez Hospital, Buenos Aires, Argentina, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research (PSR), UNAIDS, for coordinating the project.

Module 4
Safe and Effective Use of Antiretroviral Treatment

This module provides guidance primarily to clinicians, both doctors and nurses, counsellors, and managers of clinical services. Policy makers, people living with HIV/AIDS (PLHA), and mid-level decision makers in major and district hospitals, and in training institutions, may also find this guidance useful.

1. Introduction

In recent years powerful antiretroviral (ARV) treatment regimens have become available. So far, with a few exceptions, only people living with HIV/AIDS from industrialised countries have benefited from these treatments. In a proportion of patients, triple combination ARV therapies reduce viral load plasma levels to undetectable levels and have a beneficial clinical effect. HIV-related symptoms may disappear, the incidence of opportunistic infections is reduced and quality of life improves. Triple therapy has decreased dramatically the number of hospitalisations for HIV-related illness in industrialised, and some middle income, countries and prolonged the lives of many people with HIV.

However, these treatments are not a cure for AIDS and their long term effectiveness is not yet known. Resistance may develop even in patients who adhere strictly to the regimen. Combination therapy including protease inhibitors is most effective in patients who have never been treated with ARVs. In patients who have already taken ARVs however, up to 40% treatment failure has been observed after one year of treatment. HIV may persist in "sanctuary sites" where the drugs cannot suppress viral replication. Studies have shown that after 20-30 months of successful combination ARV treatment, HIV can still be isolated despite patients having undetectable HIV RNA plasma levels. This suggests that ARV treatment cannot be stopped; it is a treatment for "life" unless or until it fails, or until current regimes are superseded by new drug combinations.

Current ARV therapy is far from ideal. The regimens are complicated, requiring between 2 and 20 pills a day, they may cause severe side effects, they require close and often expensive laboratory monitoring, and there may be interactions with other drugs. Finally, the drugs themselves are very costly. In May 1998, the annual cost of triple therapy including a protease inhibitor amounts to US$ 10,000 - 15,000. ARV treatment guidelines change rapidly and differ between countries. It is expected that more powerful drugs and easier regimens will become available in the near future.

Currently available ARVs belong to two major classes of drugs: reverse transcriptase inhibitors (RTIs) and Protease Inhibitors (PIs). RTIs are further divided into Nucleoside Reverse Transcriptase Inhibitors (NRTI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI).

All these drugs target enzymes which are important for RNA replication and viral functioning. Once the HIV retrovirus has invaded a macrophage or T-lymphocyte, the enzyme HIV reverse transcriptase converts the viral RNA genome into a DNA copy, which is then integrated into the host chromosome by the enzyme integrase. A third enzyme, protease, contributes to viral functioning by catalysing the cleavage of viral core proteins for the final assembly of viable virions. Once HIV is integrated into the host DNA, the virus multiplies rapidly, creating several billion new copies a day. This inevitably results in mutations of the viral genome. Some of the mutations may confer resistance to one specific agent or to a whole class of ARVs.

In most industrialised countries eleven antiretroviral agents have been approved for treatment. Other classes of drugs are under development. (See section on specific drugs including Tables 9-14 for detailed information on each of the drugs.)

Good adherence to the ARV regimen is essential to avoid development of resistant strains. However, the regimens are complicated and adherence is difficult even in the most favourable circumstances; a very supportive environment, materially and socially, is required.

Combination therapy requires taking drugs twice or three times a day at regular time intervals. There are often adverse effects, and the drugs have to be taken for life. One of the protease inhibitors (Ritonavir) requires refrigeration and other ARVs must be taken with large quantities of water (see drug data sheets at end of the document). Patients may also have to take other drugs to prevent or to treat opportunistic infections. Adherence to such a complicated treatment for a person who has little knowledge about the disease, has many other problems, eats only when food is available and has no watch, is not an easy task. A physician who has only a few minutes per patient cannot adequately explain the regimen and support the patient's adherence. Moreover, because of the stigma associated with HIV infection, individuals may be reluctant to reveal their seropositivity to others. Therefore, except for the health care staff, no one will be able to help them to adhere to their ARV regimen.

Many clinicians do not have enough time to provide adequate counselling about HIV. If counsellors are available, they will need special training in ARVs and will work closely with the prescribing clinician. In many settings clinicians do not have enough time per consultation to explore all the client's concerns and questions about ARVs and adherence. The client may in any case feel uncomfortable discussing "non-medical" issues with his or her doctor and may prefer talking to a counsellor. The physician will have to make extra time to counsel patients on ARV treatments, and he/she may need extra training to improve counselling skills or may choose to work closely with a counsellor.

2. What needs to be in place before initiating ARV therapy

Due to their high cost , the complexity of regimens and need for careful monitoring, certain services and facilities must be in place before considering the use of ARVs in any situation.

Conditions necessary to introduce ARVs

- Access to functioning and affordable health services and support networks into which ARV treatments can be integrated so that the treatments are provided effectively.
- Information and training on safe and effective use of ARVs for health professionals in a position to prescribe ARVs.
- Capacity to diagnose HIV infection and to diagnose and treat concomitant illnesses.
- Assurance of an adequate supply of quality drugs[1].
- Sufficient resources should be identified to pay for treatment on a long term basis; patients must be aware that treatment is "for life".
- Functioning laboratory services for monitoring including routine haematological and biochemical tests to detect toxicities, must be available[2].
- Access to voluntary HIV counselling and testing (VCT) and follow up counselling services should be assured, including counselling PLHA on the necessity of adherence to treatment.

[1] See Module 8 on drug regulatory mechanisms and safeguards for storage, distribution and prescription for further details.
[2] See Module 5 laboratory requirements for safe and effective use of ARVs for further details.

Advantages and disadvantages of ARV treatment

There are advantages and disadvantages to using ARVs at *any stage* of HIV disease and it is important for the physician and patient to consider these before embarking on difficult and costly treatment.

Advantages

- A longer life.
- Disappearance of symptoms, improved quality of life in symptomatic patients, delayed disease progression, fewer opportunistic infections.
- Decreased risk of hopitalization.
- Control of viral replication.

Disadvantages

- Impairment of the quality of life in particular for the asymptomatic patient because of the difficult treatment regimen or adverse reactions.
- Development of drug resistance and cross resistance when patients are treated with a sub optimal (bi- or mono-) ARV treatment regimen, when viral load monitoring is not possible (to detect treatment failure) or when patients do not adhere to ARVs. Such resistance will limit the treatment options in the future and increase the risk of transmission of resistant strains.
- Raising false hopes in a proportion of patients who will either not respond or not tolerate the therapies.
- Potential toxicity during pregnancy.
- The cost. Money spent on ARVs is then not available for other essential items for the family, which may also improve the quality of life of the person living with HIV infection.

3. When to initiate antiretroviral therapy

As yet it is not clear when is the best time to start combination therapy. The recommendations for ARV treatment in industrialised countries are often based on virological criteria, but not on clinical outcome or quality of life data (proven clinical efficacy).

Table 1 Suggested priority to be accorded to ARV treatment according to disease stage and available laboratory facilities

Disease stage (WHO stage 1-4)	Tests available		
	No CD4 counts No viral loads	Only CD4 counts	CD4 counts Viral loads
1. Acute HIV illness	No ARVs	No ARVs	No priority
Asymptomatic phase	No ARVs	Limited priority	Limited priority
2. Early symptomatic phase	No ARVs	Limited priority*	Limited priority*
3. Symptomatic phase, non-AIDS	Limited priority**	ARVs***	ARVs***
4. AIDS	ARVs***	ARVs***	ARVs***
5. Terminal AIDS	No ARVs	No ARVs	No ARVs

* Depending on available resources, CD4 count and/or viral load results, bitherapy, or ideally tritherapy, could be considered.

** Depending on available resources bitherapy, or ideally tritherapy could be considered.

*** Start ARV treatment based on CD4 count and/or viral load results. With only a small budget it is probably best not to start too early with ARV treatment to allow the continuation of this treatment once it has been started. A maximum benefit on the quality of life of patients is expected in patients with CD4 counts < 200/mm^3 and/or a viral load > 30.000-100.000 copies/ml plasma.

3.1 Acute HIV illness

In industrialised countries ARV treatment is sometimes recommended in the acute phase of the illness. The data currently available however suggest that even with early, highly active antiretroviral therapy (HAART), eradication of HIV is not possible. Starting ARV treatment during the acute phase of the illness is very expensive as it must continue for life. Moreover, an acute HIV illness is generally not recognised in many developing countries because such episodes are difficult to distinguish clinically from other infections prevalent in these parts of the world, such as malaria or typhoid fever.

When resources are limited, there is therefore a strong case against using ARVs for this indication.

3.2 Asymptomatic patients

In most industrialised countries ARV treatment is recommended in asymptomatic patients with plasma HIV RNA levels greater than 5,000 to 10,000 copies per ml regardless of the CD4 cell count. However, even in industrialised countries, many asymptomatic patients choose *not to* take ARVs, because although there may be theoretical reasons to take ARVs, the complex and unpleasant regimes may outweigh the benefits at this stage. Furthermore many people are deciding to wait rather and remain "ARV naive" so that when more powerful, simpler and less costly drugs become available they can still benefit. ARVs often cause side effects, the regimens are complex and the long term benefits have not been demonstrated for this specific group of patients.

Disadvantages of "early combination ARV treatment" in asymptomatic HIV disease

1. In asymptomatic patients, ARVs may decrease the quality of life because side effects are common and taking large numbers of pills at regular time intervals may interfere with employment and daily activities and can be very stressful.
2. Long-term ARV treatment is very expensive.
3. Resistance may develop, reducing treatment options in the future. Long-term, strict adherence to ARV treatment may be difficult to maintain (leading to resistance).
4. Asymptomatic patients may be less willing to adhere to difficult ARVs regimens than symptomatic patients, because ARVs do not obviously improve their lives and have significant side effects.
5. Adverse consequences of some ARVs such as lacticacidosis and pancreatitis may be life threatening.
6. The long term side effects of ARV drugs remain unknown.

Treatment of asymptomatic people in resource poor countries is problematic. Firstly, it has to be determined whether an asymptomatic patient really is HIV infected. The HIV test result should therefore be reliable and accompanied by adequate counselling. Recently the World Health Organisation and UNAIDS have developed new guidelines for HIV testing *(Revised recommendations for the selection and use of HIV antibody tests, 1997).* A positive HIV test (rapid or ELISA) should be confirmed by at least one other test (also rapid or ELISA). Resources should be available to implement these guidelines.

Secondly, to decide when to start ARV treatment in an asymptomatic patient, it is recommended that a reliable CD4 lymphocyte count and viral load test be performed. Both tests require a sophisticated laboratory and trained personnel. At the time of writing a viral load test costs about US$ 100 per

test. Some commercially available viral load tests perform less well with certain HIV genotypes that are frequently seen in poor countries, though the most recent tests have largely overcome this problem.

Thirdly, in many countries the stigma associated with HIV remains high. Women are often unable to tell their partner that they are HIV seropositive because they risk being abandoned. A person may lose his/her job when it is known that he/she is HIV seropositive. People may be reluctant to accept ARV treatment because having to take so many pills is difficult to hide and may reveal their seropositivity to others. Furthermore, in poor countries with limited ARV availability, access to ARVs may be limited to symptomatic patients, as the priority group. (See Modules 2 and 3 for further details)

Thus in countries where resources for ARV treatments are limited, it may be difficult to argue for treatment for asymptomatic individuals.

3.3 Symptomatic patients

ARVs are certainly beneficial for symptomatic patients. Opportunistic infections occur less often and patients may even become completely asymptomatic for a substantial period of time. Current recommendations are however, to continue with prophylaxis against certain OIs, (such as cotrimoxazole for *pneumocystis carinii* pneumonia in industrialised countries and for pulmonary infections and septicaemia in developing countries, and isoniazid prophylaxis for TB in HIV-infected people at high risk of developing TB, especially in developing countries) even if CD4 count rises. There are many case reports of patients with CMV, cryptosporidiosis, wasting or chronic diarrhoea whose symptoms have resolved after starting triple therapy.

Disadvantages of ARVs in symptomatic patients in poor resource settings.

1. There are particular problems in prescribing ARVs to patients who are taking certain anti-tuberculosis drugs (see section on TB and ARVs). However, there is no contraindication to taking ARVs with standard isoniazid TB preventive therapy.
2. Symptomatic patients may have more difficulty tolerating ARVs than asymptomatic patients because they already have symptomas such as nausea because of gastro-enteritis. Adverse events may also occur more often in symptomatic patients because of pre-existing liver disease, polyneuritis or renal insufficiency.
3. ARVs interact with certain drugs used to treat opportunistic infections.

Despite these possible disadvantages, treatment of symptomatic patients is the norm in industrialised countries. In developing countries where resources are available for ARV treatment, treatment of symptomatic patients should take priority over treatment of asymptomatic patients.

3.4 Terminal HIV and palliative care

Patients with terminal HIV disease, such as widespread malignancy and patients who are severely immunocompromised (CD4 <10) will rarely respond to ARV therapy and initiating therapy at this stage may be a waste of limited resources and a burden to the patient. As stated earlier, ARV therapy should be provided in the context of a continuum of care for PLHA. If treatment fails or patients have terminal HIV and do not respond to ARV therapy, adequate palliative care and emotional and spiritual support should be provided. Referral to a home based care team, if available, for management of pain and symptomatic relief is important if the patient chooses not to remain hospitalised. It is also important to have bereavement counselling available for carers and family members.

4. ARV treatment in clinical practice: the steps to follow

Table 2 lists the steps that should be followed by the clinician when considering initiating ARV therapy at any stage of HIV disease.

Table 2

ARV treatment in clinical practice

1. HIV pretest counselling

2. Obtaining informed consent

3. HIV testing

4. HIV post test counselling

5. Medical consultation

- **medical history**
- **physical examination, including weight**
- **STD screening**
- **TB screening (ideally including a chest Xray)**
- **routine haematological and biochemical tests**
- **other tests to diagnose opportunistic infections if indicated**
- **pregnancy test if indicated**
- **CD_4 lymphocyte count (highly recommended), viral load (if available)**

6. Follow-up visit to discuss

- **results of medical check-up**
- **treatment options including the risks and benefits of ARV treatment**

7. Choose the optimal ARV treatment regimen and explain it in detail.

8. Provide the ARVs and organise drug counselling in order to obtain optimal adherence.

9. Provide ongoing counselling including advice on safer sex and family planning

10. Monitor the ARV treatment : clinically, biologically, and for adherence.

5. Which antiretroviral regimen to initiate

5.1 Triple combination therapy

The treatment of choice is triple combination therapy including at least one protease inhibitor with potent *in vivo* activity (indinavir, ritonavir, nelfinavir and the new formulation saquinavir). An alternative may be triple combination therapy with ritonavir, saquinavir and an NRTI. Less potent regimens are 2 NRTIs + 1 NNRTI. It is generally recommended that the combination should include a drug that penetrates well into the brain such as zidovudine or stavudine.

Nucleoside analogue combinations that could be used in triple therapy are:

- zidovudine (ZDV) + didanosine (ddI)
- zidovudine (ZDV)+ lamivudine (3TC)
- stavudine (d4T) + lamivudine (3TC)
- stavudine (d4T) + didanosine (ddI)

The above are roughly equivalent. Zidovudine (ZDV) and zalcitabine (ddC) in combination are less active and are regarded as second tier.

Certain combinations are *not* advisable, because of overlapping toxicity:

- didanosine (ddI) + zalcitabine (ddC)
- stavudine (d4T) + zalcitabine(ddC)

or because of an antagonistic effect due to overlapping intracellular phosphorylation pathways:

- zalcitabine(ddC) + lamivudine(3TC)
- stavudine(d4T) + zidovudine (ZDV)

Table 3 Examples of triple therapy regimens including a protease inhibitor

Initial regimen	Alternative combination
ZDV + 3TC + PI_1*	D_4T + DDI + PI_2** Ritonavir + Saquinavir + NRTI
D_4T + 3TC + PI_1	ZDV + DDI + PI_2 Ritonavir + Saquinavir + NRTI
ZDV + DDI + PI_1	D_4T + 3TC + PI_2 Ritonavir + Saquinavir + NRTI
D_4T + DDI + PI_1	ZDV + 3TC + PI_2 Ritonavir + Saquinavir + NRTI

5.2 Double combination therapy

Double combination therapy (2 NRTIs) produces clinical and virological improvement, but is inferior to triple therapy . However, many patients in industrialised countries continue to take bitherapy either because they do not want to take more complicated tritherapy regimes or because they do not want to "use up all their options." Double therapy could also be considered if patients do not tolerate triple combination regimens or if there are contraindications for the use of protease inhibitors. Double therapy can also be used where protease inhibitors are not available or affordable. Double combination therapy with 2 NRTIs is generally well tolerated and is easier to monitor than triple combination therapy.

When double therapy with two nucleoside analogues is failing, adding only a protease inhibitor without changing the NRTIs (because alternative ARVs drugs are not available) may lead to rapid resistance against protease inhibitors since the protease inhibitor then behaves as monotherapy. Double combination of one NRTI and one protease inhibitor has a stronger antiviral effect but also leads to resistance against the protease inhibitor.

6. How to monitor ARV treatment

It is advisable for patients on triple therapy to be seen monthly; particularly at the start of treatment. Once stabilised, patients may then be seen every three months. At each visit, side effects and adherence to the treatment should be discussed in depth. At the start of treatment, routine haematological and biochemical tests should be done monthly to detect potential side effects. Careful monitoring is needed particularly in patients who abuse alcohol or are infected with hepatitis B or C,

* PI with potent in vivo activity : indinavir, ritonavir, nelfinavir

** The best alternative PI after failure on an initial PI containing regimen is unknown. Cross-resistance between indinavir and ritonavir is almost total.

who have abnormal liver function, and in patients with abnormal renal function. The appearance of certain symptoms such as nausea, anorexia or abdominal pain is a reason for repeating certain laboratory tests.

Ideally, *if available*, viral load and /or CD4 count should be measured regularly, e.g., in untreated patients every 6 - 12 months and in patients on ARVs every 3 - 6 months.

The results of viral load testing should be interpreted with caution. Certain viral strains that are particularly frequent in developing countries may be difficult to detect with commercially available testing methods; and viral load levels may vary according to the technique that has been used, the laboratory where the test has been done, the time and the way the sample was transferred to the laboratory. Levels may increase after a recent infection or vaccination. An increasing viral load does not necessarily mean that the ARV treatment is not effective. It may be that the patient is not adhering to the treatment. There may also be problems in measuring CD4 counts in developing country settings (for further details on laboratory monitoring see Module 5).

Treatment decisions should take into account these possible variations and the clinical condition of the patient, information about adherence and availability of ARVs to which he/she could switch. Ideally a viral load measurement should be done before starting and before changing ARV treatment; and 1 to 2 months after the start of the initial or new treatment. Where viral load testing is not available CD4 counts can be used instead to guide initiation and monitoring of ARV treatment. CD4 lymphocyte counts are also used to decide whether the patient should receive prophylactic treatment against opportunistic infections. Ideally, in countries where ARVs are introduced, a reference laboratory should be established where these tests could be performed (see Module 5 for further details).

In developing countries where CD4 counts or viral loads are not routinely available, clinical indicators such as weight and total lymphocyte count will give some indication of disease progression and treatment response.

Table 4 Laboratory monitoring during ARV treatment

	Bitherapy	**Tritherapy** (including a protease inhibitor)
Haematocrit/haemoglobin	**X**	**X**
White blood cell count + differential	**X**	**X**
Platelets	**X**	**X**
Bilirubin	**X**	**X**
Transaminases	**X**	**X**
Amylase	**X**	**X**
Creatinine/Urea/Urine proteinalysis	**X***	**X****
Creatinine phosphokinase	**X***	**X****
Glucose/Glucose urine analysis		**X****
Triglycerides		**X****
CD_4 lymphocytes count	**X****	**X****
Viral load		**X***

* Advisable, but not essential

**Highly recommended, but not essential

7. Changing antiretroviral therapy

7.1 When to change?

Reasons for changing ARV treatment are: treatment failure, toxic effects, intolerance, non-adherence, and current use of a sub-optimal treatment regimen (Table 5). In industrialised countries definitions of treatment failure are based on viral load measurements - a rising plasma viral RNA level or failure to achieve the desired reduction in plasma viral load. A declining CD4 count is also an indication to change treatment (see Module 5 for further details). In settings where it is not possible to do viral load tests and CD4 counts, weight loss and other clinical changes may provide a good indication of the need to change treatment.

Asymptomatic patients currently taking double NRTI combination treatment with undetectable plasma HIV RNA levels should be closely monitored. If plasma HIV RNA levels increase above 5,000 to 10,000 copies per ml, the treatment regimen should be changed. In the absence of laboratory facilities to measure viral load, decisions to change treatments should be based on results of CD4 lymphocyte counts and/or clinical condition, including weight of the patient.

Factors other than viral resistance that can lead to loss of viral suppression are: non-adherence to treatment and intercurrent illnesses. To evaluate the efficacy of an ARV regimen, viral load should not be measured in the days following a vaccination. If during ARV treatment a patient develops side effects, the offending drug should be replaced by another drug with a different toxicity profile. If the cause of the side effects is not clear, a brief and complete interruption of the full therapeutic regimen is generally preferred. Because ARVs may have to be changed it is not ideal to start ARV treatment when only a limited number of ARVs are available - often the case in developing countries. If the ARV drug is stopped because of intolerance or side effects and no alternative treatment is available, resistance may develop rapidly.

Table 5 Indications for changing therapy

1. Treatment failure :

Clinical disease progression

Declining CD4 count

Failure to achieve the desired reduction in viral load *:*

viral response = reduction of viral load > 2 log HIV RNA copies (100 fold) or viral load levels below detectable levels

Rising plasma viral load

viral load rebound to 0.5 log HIV RNA copies above the level of maximum virological response (nadir)

2. Unacceptable toxicity, intolerance or non-adherence

3. A sub-optimal treatment regimen : e.g. ARV monotherapy

7.2 What to change to?

When treatment failure occurs all drugs in the regimen should be changed if possible, because it is currently impossible to determine which of the combination's drugs is the one to which resistance has developed. Changing both drugs in a double NRTI combination regime or changing a protease inhibitor and a NRTI in a three-drug combination is advised. Simply adding a protease inhibitor or any other drug to a failing regime is never recommended.

Table 6 Predicting the effectiveness of switching therapy

Switching combinations		Likely effectiveness
Switching NRTI combinations		
ZDV+3TC →	d4T+ 3TC	probably not effective
d4T+ddI →	ZDV+3TC	may be effective
ZDV+ddI →	d4T +3TC	may be effective
ZDV+3TC →	d4T+ddI	may be effective
Switching protease inhibitors*		
nelfinavir →		may be effective
ritonavir/saquinavir →		may be effective
ritonavir/saquinavir →	nelfinavir	probably not effective
ritonavir/saquinavir →	indinavir	may be effective
indinavir →		probably not effective
ritonavir/saquinavir →		probably not effective
indinavir	nelfinavir	
nelfinavir	indinavir	

* **There is a great deal of cross resistance between the protease inhibitors, therefore switching protease inhibitors in cases of treatment failure is rarely successful.**

When changing because of non-adherence, the reasons for non-adherence must be explored. For example, if a patient does not like to take three times daily (tds) regimen, a twice daily (bd) regimen may be proposed. If a change in therapy is needed because of drug toxicity, only the drug causing the toxicity should be replaced.

8. Special considerations

8.1 ARV treatment in women of childbearing age

Before considering ARV treatment in a woman, a pregnancy test may be required. Data on ARVs in pregnancy is limited, particularly in the first trimester. A study in the USA is currently assessing potential foetal risks. So far we know that zidovudine given in the second or third trimester does not

cause congenital malformations. The long-term effect of zidovudine on the child's health remains unknown. As regards the other ARVs, very little is known about their potential toxicity for the foetus (see Module 6 for more details).
Triple therapy, therefore, should probably not be prescribed for women during early pregnancy or for women at risk of pregnancy. Contraception is recommended for all women considering combination ARV treatment. When a woman treated with bi- or triple combination therapy becomes pregnant, the risks of such treatment for the foetus should be discussed. The physician or counsellor should discuss family planning with all women before starting ARVs.

If a woman becomes pregnant whilst taking ARVs the counsellor will have to help her decide whether to continue with the pregnancy or whether to have a termination, if this is available. The desire to have a child for many women is of great importance and may override medical concerns. Once the decision has been made to have a baby or to continue with a pregnancy this decision should be supported by the counsellor and ARV therapy may have to be modified during this period. The possible detrimental effects to the mother of altering her ARV treatment during pregnancy must also be discussed.

8.2 ARV treatment in children with HIV (see Module 6 for further details on ARVs to reduce mother-to-child transmssion).

In infected children in industrialised countries ARV treatment is continued after birth particularly in children with a poor prognosis (high viral load, symptomatic). If a child becomes infected despite zidovudine prophylaxis, ideally the zidovudine treatment should be replaced by a new ARV treatment regimen. In poor resource countries PCR testing is generally not available to confirm an early diagnosis of HIV infection. ARV treatment for children should only be considered if a definite diagnosis of HIV is made.

Experience with triple therapy including a protease inhibitor in children remains limited. However early reports are encouraging and ARVs may be indicated, particularly for symptomatic children. So far only a few licensed ARVs are available in paediatric formulation: ritonavir syrup which is difficult to tolerate and nelfinavir powder which is not widely available. For the moment no indinavir syrup is commercially available. Obtaining good compliance with ARVs may be particularly difficult with children. Monitoring ARV treatment in children < 1 year old requires extra expertise. CD4 lymphocyte counts in children are much higher than in infected adults. Viral load is also generally higher in children.

8.3 HIV-2 infection

All the ARVs are effective against HIV-2 infection except the NNRTIs. ARV treatment with potentially toxic drugs is probably not appropriate in asymptomatic people with HIV-2 infection as HIV-2 infection progresses more slowly than HIV-1 infection. The monitoring of ARV treatment in people with HIV-2 infection is also complicated by the fact that there are no commercially available tests to measure viral load.

8.4 ARVs in patients with tuberculosis

In HIV infected patients being treated for tuberculosis, protease inhibitors increase the serum levels of rifampicin. On the other hand, rifampicin decreases the level of protease inhibitors. Therefore HIV infected tuberculosis patients should have double therapy without a protease inhibitor or no ARV therapy until TB therapy is complete. (Table 7). Before considering ARV treatment, patients should be screened for active tuberculosis infection, with at least a sputum examination and a chest X-ray.

TB preventive therapy (TBPT) has been shown to reduce the incidence of TB in people with HIV. The most commonly used regimen, isoniazid, is not contraindicated if patients are taking ARVs. Rifampicin containing TBPT should, however, be avoided.

In resource poor countries it is probably better to delay ARV treatment in TB patients because it complicates the TB regimen and may decrease adherence leading to inadequate TB treatment.

Table 7

Patients with active tuberculosis : Possible ARV treatment options
1. No ARV treatment during rifampicin treatment
2. Bitherapy (no PI) during rifampicin treatment
3. Tritherapy (including indinavir) but replacing rifampicin by rifabutin 300 mg/daily
4. Tritherapy with 2 NRTI + 1 NNRTI plus routine TB treatment
5. Start tritherapy including a protease inhibitor only during the 'the continuation phase' of the TB treatment with an ethambutol-isoniazid treatment regimen.

8.5 What should not be done

- Starting ARV treatment in a person in whom an HIV diagnosis has not been confirmed.
- Promising ARV treatment when its continued, long term provision cannot reasonably be guaranteed.
- Starting ARV treatment in a patient not motivated to follow such treatment or in a person who is unaware of his/her seropositivity.
- Prescribing ARV monotherapy unless it is for the prevention of perinatal HIV transmission and post exposure prophylaxis (PEP).
- Starting ARV treatment without a minimum of laboratory monitoring. In resource poor countries anaemia with haemoglobin levels 7 to 8 gram per decilitre is relatively frequent. These patients may be particularly at risk for severe anaemia during zidovudine and cotrimoxazole treatment. Chronic hepatitis caused by hepatitis B and C infections are also very prevalent in poor resource countries. ARVs are all potentially hepatotoxic and should be prescribed with caution to these patients. If these drugs are given, liver function should be monitored at regular intervals. In cases of renal insufficiency, dosage of certain ARVs such as stavudine and indinavir should be modified.
- Starting ARV treatment without providing adequate information about how and when to take the drugs, potential side effects and interactions with other drugs, when to stop the drugs, etc.
- Providing ARV treatment without the capacity to diagnose, treat or prevent opportunistic infections such as tuberculosis and toxoplasmosis (such as isoniazid for the prevention of tuberculosis, cotrimoxazole for the prevention of *Pneumocystis carinii* pneumonia and toxoplasmosis, for patients with severe immunodeficiency).
- Providing ARV treatment without capacity to meet patient's other needs such as sufficient nutritional support, adequate home care, etc.
- Continuing ARV treatment despite serious side effects; if treatment is not stopped or changed there may be irreversible damage.

9. Counselling for ARV therapy

The psychosocial aspects associated with deciding whether to start and then continue on ARV treatment are as important as the medical aspects. Counselling for ARVs is often time consuming and physicians may choose to work with a trained counsellor with specialised skills. If appropriate and informed decisions are to be made, and treatment is to be provided safely and effectively, counselling services must be available to people living with HIV/AIDS (PLHA). Those who make the decision to start ARVs will need information, support and encouragement on a regular and long term basis in order to maintain adherence to the regimen.

Where ARVs are readily available, the possibility of obtaining these treatments is an incentive to seek out counselling and testing. It has been shown that one of the main barriers to knowing one's HIV status, particularly in high prevalence areas, is the lack of perceived benefit for those who fear they might be seropositive.

Counsellors and clients will be dealing with very different psychosocial and material problems depending on the setting[3]. Where ARVs are not available or are prohibitively expensive, knowledge of these treatments may create additional stresses, for both the client and the counsellor. In such situations, counsellors will be helping clients cope with the anguish of knowing that a treatment exists which is not accessible to them. Where ARVs are provided routinely, counselling will focus on encouraging correct use, coping with a return (albeit temporary) to a more healthy and productive life, and overall emotional well-being. In settings where the client and his/her family will be investing large sums of money in the drugs, problems relating to this use of scarce resources will have to be discussed.

ARVs have received a large amount of favourable coverage in the popular press. Even in low income countries many people with HIV are knowledgeable about ARVs and have unrealistic expectations about their availability and their efficacy. It is very important for the counsellor to inform the client about the likely availability of ARVs - in both pre- and post test counselling.

After receiving a positive result, the client will need emotional support from his or her counsellor, in addition to information about many aspects of treatment and prevention. Discovering one is HIV seropositive is traumatic and marks the beginning of a difficult psychological adjustment for the client. Psychological distress and depression may be alleviated by sensitive counselling. Several counselling sessions may be needed initially for the client to cope with their positive status *in addition* to understanding the implications of ARV therapy and its monitoring. Even in countries where ARVs are readily available many patients testing seropositive will not be at a stage of disease to warrant or desire ARVs and this will need careful discussion.

Whatever decision is made about taking antiretroviral drugs, comprehensive care and social support need to be ensured on a long term basis, to identify, prevent and treat opportunistic infections and to deal with social and family problems. This may require collaboration between medical and social services in public, private and NGO sectors.

9.1 Confidentiality and sharing HIV results

The disruption of life style brought about by complicated ARV regimens should not be underestimated. Involving a partner or significant other in ARV treatment will make taking ARVs much simpler. The counsellor should encourage sharing HIV results with a partner or close relative so that the burden of the drug taking schedule can be understood and shared. The counsellor should stress the importance of informing partners of the risk of HIV transmission and taking protective action.

In many countries, women risk being abandoned if their positive status is discovered; it is frequently the partner who has infected the woman and overall it may be better not to disclose her status. The clients' own perception of the risks and benefits of the particular situation should be respected. However, many health workers feel they have a duty to inform and thereby protect a possibly uninfected partner and that this duty is greater than the duty to protect confidentiality of the client. These are ethical issues which remain unresolved. Certainly in countries where the infected and abandoned partner will *not* be left destitute and where people can easily take preventive measures, some people would feel that there would appear to be no justification for protecting confidentiality over risk of transmission of a fatal infection.

[3] for additional information see UNAIDS Technical Update November 1997 on Counselling and HIV/AIDS

9.2 Financial commitment

Discussing how the drugs are going to be paid for, is very important. In many developing countries the only option is for the patient or his/her relatives to pay for treatment. They may think that they need only take ARVs for a few months, or intermittently when they have funds. If relatives are paying, they may have to be involved - again to make decisions about willingness to pay for treatments indefinitely and the need for a consistent supply of drugs. These decisions may be very painful and difficult, but need to be thought through before embarking on treatment.

9.3 Particular challenges

Complicated drug taking schedule:

The counsellor will have to deal with many of the problems associated with complex life long therapy. A "drug time table" helps clients to organise their drug taking schedule.

Table 8 Example of a daily drug regimen

Time	Meal	Drug	Tablets	Comments
07:00		Indinavir Isoniazid	2 1	Need to set alarm
08:00	meal	Zidovudine Lamivudine Cotrimoxazole	1 1 1	
13:00	meal			
15:00		Indinavir	2	
21:00	meal	Zidovudine Lamivudine	1 1	
23:00		Indinavir	2	Forced to stay awake

Not a cure: The counsellor must ensure that the client is fully aware that ARV therapy is not a cure, and that the drugs must be taken for the remaining time the client has to live, or until they are too sick to take them any longer. He/she should ensure that the client understands that ARVs are new drugs and no one knows whether their short term benefits, which are often great, will continue in the long term. The counsellor needs to provide accurate up to date information about the possible positive and negative outcomes of treatment, taking into account all personal and contextual factors which may influence the outcome.

Adverse effects: Adverse effects are common in the first few weeks of ARV treatment. The counsellor should be aware of these and reassure the client that these initial adverse effects will usually lessen with time. The counsellor should also be able to help the client distinguish between potentially serious and non-serious signs and symptoms.

Disruption of life style: Dietary changes may need to be made as many of the drugs are affected by the presence and types of food eaten. Meals often have to be planned carefully around the drug regimen. This can be inconvenient and disrupt family and social life. If the counsellor can involve the family in discussions about these issues, it will help them to understand the importance of timing meals and

changing routines. The counsellor may have to take time to work out a "meal and drug taking time table" that fits in with the client's and the family's life style. Client and counsellor should also discuss what to do if a dose is missed or a meal time rearranged.

Coping with "health": Taking ARVs will be for life, and once stabilised on a particular regime, the client may feel very well. This may be particularly true for people who were symptomatic prior to ARV therapy. They may be well enough to resume more of their previous lifestyle - going back to work and taking up previous hobbies or activities that were impossible before. Paradoxically, some people find the adjustment to "health" after a prolonged period of ill health difficult. Friends and family may continue to treat them as a patient despite them feeling well. The new situation and perspective will require understanding and adjustment on the part of the patient and the family.

Guilt: Some people describe feelings of guilt about taking ARVs. They may have lost partners or friends because ARVs were unavailable or could not be afforded. Many people are painfully aware of the enormous sacrifices that their friends and/or family are making to provide ARVs for them.

Coping with a "medicalised" life style: People with HIV who are asymptomatic when they start taking ARVs may resent the constraint that taking the drugs imposes on their lives. This has to be acknowledged and explored when starting ARVs. People who feel unable to embark on the strict regime that ARVs will impose on them may do better to postpone treatment.

Coping with treatment failure: Although the short term follow up of people on ARVs often results in remarkable improvement in symptomatic patients, this improvement is not universal. Furthermore, symptomatic improvement may not last long, particularly if resistance to ARVs develops, or the patient has previously been on sub-optimal ARV therapy. In developing countries, some people with HIV will put off starting ARV therapy, because of the prohibitive cost, until the last possible moment. They may by this stage be severely immunocompromised. People who have very low CD4 counts, or are terminally ill, when they start on ARV therapy tend to respond less well.

The counsellor will have to support them through the disappointment of treatment failure and balance optimism and realistic caution. Depression and despair are common when CD4 counts do not go up or weight is not gained as has been predicted or read about. This may be made worse when the client is aware of the draining of his or her financial resources into a treatment that may be futile. There may be a time when the client and counsellor will have to discuss ceasing treatment and preparing for death. There is no place for antiretroviral drugs in palliative care for severely ill patients.

9.4 Adherence issues

Combination therapy involves taking between four and 20 capsules/tablets a day depending on the regimen prescribed. Understanding how to take the drugs and the importance of not missing doses should be explained by the counsellor. The information about HIV is complicated and often confusing for clients and should be followed up with written, or clearly illustrated, instructions for future reference.

There should be open access to a counsellor for information as the need arises, and if possible, involvement of a partner or significant other, to help remind the patient about taking drugs and watching out for adverse effects. It is also important that the client understands the need for careful monitoring by a doctor and regular medical check ups.

How to improve adherence to ARV treatment?

1. Treatment decisions should be made jointly between the patient and the clinician after careful discussion of :
   - the advantages and disadvantages of ARV treatment
   - different treatment options
   - possible adverse reactions
   - the cost of the treatment
   - the need for a long term emotional and financial commitment.
2. Choice of ARV treatment regimen should take into account the life style of the patient :
   - certain patients may accept a twice daily (bd) (a regimen containing ritonavir) but not a three times daily (tds) treatment regimen (a regimen containing indinavir)
   - certain patients will be unable to store their ARV treatment (ritonavir) in a refrigerator
   - certain patients who eat at irregular time intervals may have problems taking indinavir every 8 hours on an empty stomach, 1 h before or 2 h after a meal.
3. Once an ARV treatment regimen has been chosen it should be explained very carefully:
   - how and when the drugs should be taken: written information should be provided for the patient or a family member if they are able to read. Clearly illustrated materials should be provided if the patient is unable to read.
   - what the potential adverse reactions of such treatment may be and what to do about them.
   - how and where the patient can get information about potential problems with the ARV treatment.
   - when the patient should come back for follow-up visits, and monitoring of blood tests.
   - who will help the patient to adhere to the treatment regimen: partner, another family member, a friend, a nurse. For certain patients where adherence problems can be expected, ARV treatment might need to be directly observed (DOT).
   - where to get psychosocial support.
4. Patients should be able to consult regularly with a trained counsellor to discuss all aspects of adherence.
5. There should be a reliable, long-term and regular supply of ARVs and patients should have easy access to these ARVs.
6. Communication skills of the doctor/counsellor are of great importance. Unless adequate rapport is established with the patient, adherence may be jeopardised.

9.5 ARVs must not detract from HIV prevention messages

People who take ARVs will understand that the aim of this medication is to lower the amount of virus in their blood, often to undetectable levels. They may conclude that if their viral load is very low they do not need to use protective measures to prevent HIV transmission. There have been anecdotal reports of people abandoning condom use when on ARVs. The counsellor should stress that the virus can still be transmitted and that safer sex should continue.

Alcohol and recreational drugs

There is limited information on how any of the ARVs interact with alcohol or recreational drugs. A study looking at factors that influenced HIV disease progression in long term survivors found that cannabis use, diet, and alcohol consumption, did not significantly influence disease progression. Therefore counsellors should advise that moderate alcohol intake and cannabis smoking are not contraindicated. People taking ARVs should be encouraged to lead as normal a life as possible. However, there is evidence that many recreational drugs (for example "ecstasy", amphetamines (speed) and diazepam (Valium)) interact with PIs (especially ritonavir). Any client taking recreational drugs should be encouraged to discuss this with his/her counsellor.

To the extent, however, that alcohol and any other drugs may make people less alert and responsible and therefore less able to adhere to the regimen, excessive use should be discouraged.

Support groups

Many people with HIV have found mutual support in groups of people living with HIV, very helpful. When embarking on ARV therapy it may be useful to be in contact with other people who are having similar treatments, share experiences and discuss overcoming problems associated with taking ARVs. Support groups for other medical conditions such as breast cancer have been shown to significantly improve prognosis. Clinicians and counsellors need to be aware of support groups in their area and proactively refer patients.

Counsellor support

Counselling people with HIV can be very stressful for the counsellor, especially when looking after clients and their families when a treatment fails. Regular supervision and a counsellor support group to share complicated or distressing cases provide valuable support.

Antiretroviral drugs

As all ARV drugs are relatively new, their adverse effects are still being monitored. It is very likely that additional adverse effects and drug interactions will be identified.

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

(Tables 9 and 10)

Zidovudine (ZDV) often called AZT.

(Trade name Retrovir)

Zidovudine is an analogue of the nucleoside thymidine. After the drug is phosphorylated by cellular enzymes it competitively inhibits the incorporation of thymidine into the proviral DNA. The drug inhibits the prolongation of the DNA chain by preventing the addition of further nucleosides. Penetration into the cerebrospinal fluid is about 50 - 70 % of plasma levels.

Dosage and administration

250 or 300 mg bd orally
200mg tds orally
In patients with AIDS dementia complex a dosage up to 1 g a day can be considered.
Zidovudine can be taken with food or on an empty stomach but taking it with food may reduce feelings of sickness.

Adverse effects

Nausea, headache, muscle pain, skin rashes, insomnia and fatigue occur relatively frequently when starting zidovudine treatment. In most patients these complaints disappear within the first six weeks of therapy.
Haematological toxicity may develop within one month of the start of the zidovudine treatment, but generally anaemia occurs in patients with advanced disease. In patients without symptoms treated with 500-600 mg a day, haematological toxicity is rare (severe anaemia in 2% of the patients after 18 months of treatment). The mean corpuscular volume of red blood cells will increase in all patients receiving zidovudine. Long term use of zidovudine may lead to myopathy which may be preceded by an increase in creatine phosphokinase. In most patients, myopathy is reversible within 8 weeks of stopping the zidovudine therapy. Fatty liver and lactic acidosis have occasionally been reported: zidovudine should be stopped in patients with progressive hepatomegaly or if amino transferase levels rapidly increase. Bluish pigmentation of nails and mucosa is another uncommon adverse reaction.

Drug interactions

Zidovudine should not be given with stavudine because of viral antagonism. Zidovudine may cause bone marrow suppression and must be used with caution with other drugs commonly used in HIV disease such as cotrimoxazole (septrin) and gancyclovir that also cause neutropenia and anaemia.

Contraindications/precautions[4]

Do not start zidovudine in the presence of severe anaemia (haemoglobin < 7g/dl) neutropenia or leucopenia (neutrophils/leukocytes < 750/mm^3).
Combination with other potentially haematotoxic drugs such as cotrimoxazole (septrin), pyrimethamine and ganciclovir should be avoided.
Stop zidovudine if haemoglobin levels decrease below 7 g/dl, if neutrophils/leukocytes < 750/mm^3 or if persistent myalgia.

Didanosine (ddI)

(Trade name Videx)

Didanosine is an adenosine analogue. In contrast with zidovudine and stavudine, didanosine (as well as zalcitabine and lamivudine) has a greater activity in resting peripheral mononuclear cells infected with HIV than in activated cells.

[4] Precautions when prescribing **all** ARVs during the first trimester of pregnancy (patient must be fully informed of possible risks compared to benefits). See Module 6 for details of prescribing ARVs during pregnancy.

Didanosine is rapidly destroyed by exposure to acid. Tablets therefore contain an antacid to prevent drug degradation and to maximise bio-availability.

Dosage and administration
200 mg bd orally for a person ≥ 60 kg
125 mg bd orally for a person < 60 kg
400mg od/250-300 mg od <60 kg
Tablets should be taken on an empty stomach. No food should be taken for 1 hour afterwards The tablets must be dispersed in water, chewed or crushed thoroughly before swallowing. The flavour of the dissolved tablets can be improved by adding clear apple juice.

Adverse effects
No haematological side effects.
Minor side effects such as nausea, vomiting, diarrhoea, skin rashes, headache, itch and lethargy have been reported but these usually settle after the first 6 weeks of treatment.
The major toxicity is a dose related, predominantly sensory, symmetric polyneuropathy. This neuropathy is generally reversible within weeks of stopping treatment. If the didanosine however is continued too long the polyneuropathy may become irreversible (the same is true for the other neurotoxic ARVs)

Another potentially serious toxicity is pancreatitis. Fatalities from ddI induced pancreatitis have been reported. Xerostomia has been reported in up to 10 % of patients. Other adverse reactions include gastrointestinal intolerance, hepatitis, hyperuricaemia and gout.

Drug interactions
The antacid in the didanosine tablets can reduce the absorption of ketoconazole and dapsone. These drugs should therefore be taken with food and several hours apart from the didanosine. Oral ganciclovir may increase the absorption of didanosine and therefore increase the risk of didanosine toxicity. ddI seriously reduces the serum level of ganciclovir. For these reasons it is best not to prescribe didanosine with ganciclovir. The use of quinolones is also contraindicated because the divalent cations in the buffer can interfere with absorption.
Didanosine may also decrease the absorption of protease inhibitors. Therefore **PIs should be taken at least 2 hours before taking didanosine.**

Contraindications/precautions
Caution is needed when didanosine is given to patients with a history of peripheral neuropathy or to patients already taking neurotoxic drugs.
Patients with advanced HIV disease, with a history of pancreatitis or who are taking other drugs or excessive alcohol that may also cause pancreatitis are at an increased risk. If the patient develops pancreas specific serum amylase levels greater than twice the normal level, stopping the didanosine should be considered.

Zalcitabine (ddC)
(Trade name Hivid)
Zalcitabine is a cytidine analogue.

Dosage and administration
0.75 mg tds orally for a person ≥ 40 kg
0.375 mg tds orally for a person < 40 kg
The absorption of zalcitabine is slightly better when taken with a meal.

Adverse effects
Polyneuropathy is more common with zalcitabine than with didanosine. It is also a dose dependent sensory, symmetric peripheral neuropathy, usually involving the lower limbs initially. The neuropathy is generally reversible after stopping treatment. If, however, the drug is not stopped in time, symptoms of polyneuropathy may persist.
Zalcitabine may cause stomatitis, mouth ulcers, nausea and vomiting, gastro-intestinal upsets, headaches and anorexia. Pancreatitis is less often observed than with didanosine.

Contraindications/precautions
Caution is needed when zalcitabine is given to patients with a history of peripheral neuropathy or to patients already taking neurotoxic drugs. Some drugs used in HIV disease can increase the risk of developing peripheral neuropathy. These include stavudine (d4T), dapsone and isoniazid, and therefore should be avoided in combination.
Caution is also needed for patients with a history of pancreatitis or who are taking other drugs or excessive alcohol that may cause pancreatitis. If a patient develops pancreas specific serum amylase levels greater than twice the normal level, stopping the zalcitabine should be considered.

Stavudine (d4T)

(Trade name Zerit)
Stavudine is a thymidine analogue. Stavudine also penetrates well into the CSF.

Dosage and administration
40 mg bd orally for a person ≥ 60 kg
30 mg bd orally for a person < 60 kg
The absorption of stavudine is slightly better when taken with a meal but it can be taken at any time.

Adverse effects
Similar peripheral neuropathy as with didanosine and zalcitabine is seen. Pancreatitis and hepatitis have also been described. There is an increased risk of pancreatitis in patients treated with pentamidine or ganciclovir. Other side effects include nausea and vomiting, fever, headache, skin rashes, diarrhoea and lethargy.

Contraindications/precautions
Caution is needed when stavudine is given to patients with a history of peripheral neuropathy or patients already taking neurotoxic drugs, in particular ddC, dapsone and isoniazid.
Caution is also needed for patients with a history of pancreatitis or who are taking other drugs or excessive alcohol that may cause pancreatitis. If a patient develops pancreas specific serum amylase levels greater than twice the normal level, stopping the stavudine should be considered.
Zidovudine should not be given with stavudine because of mutual antagonism.

Lamivudine (3TC)

(Trade name Epivir)
Lamivudine is a cytidine analogue. Rapid development of resistance is seen when used as monotherapy (causes a mutation in the HIV polymerase gene at codon 184, but lamivudine resistant strains with this mutation remain sensitive to zidovudine).

Dosage and administration
150 mg bd orally
The absorption is slightly better when lamivudine is taken with a meal.

Adverse effects
Very well tolerated. Occasionally headache, fatigue, insomnia, nausea, abdominal pain and peripheral neuropathy. Pancreatitis has been reported in children.

Contraindications/precautions
No drug interactions have been described

Table 9 : Nucleoside reverse transcriptase inhibitors

Drug Generic (trade) name	Form	Dosage	Route/conditions	Adverse events	Unit cost in US $*	Annual Cost in US $*
Zidovudine (ZDV or AZT) (Retrovir®)	T : 100, 250, 300mg A : 200 mg S : 1 ml = 10 mg	300 mg bid 100-120		headache nausea malaise anaemia neutropenia myopathy	1.5/100 mg	2,738
Didanosine (ddI) (Videx®)	T : 25, 50, 100 mg P : 150 mg	≥ 60 kg 200 mg bid < 60 kg 125 mg bid	Empty stomach Tablets must be chewed or crushed thoroughly before swallowing	polyneuritis pancreatitis abnormal liver tests	1.44/100 mg	2,102
Zalcitabine (ddc) (Hivid®)	T : 0,375, 0,750 mg	≥ 40 kg 0,750 mg tid < 40 kg 0.375 mg tid		polyneuritis pancreatitis stomatitis oral ulcers	2.4/0.75 mg	2,640
Lamivudine (3TC) (Epivir®)	T : 150 mg S : 1 ml = 10 mg	150 mg bid		well tolerated, pancreatitis in children neutropenia anaemia (when given with ZDV)	3.6/150 mg	2,572
Stavudine (D_4T) (Zerit®)	T : 30, 40 mg S = 1 ml = 1 mg	≥ 60 kg 40 mg bid < 60 kg 30 mg bid		polyneuritis pancreatitis abnormal liver tests	3.9/40 mg	2,788

T : tablet, A : ampoule, S : solution, C : capsule, P : powder

*costs at time of writing

Table 10

Interactions between nucleoside analogues and other drugs: prevention, monitoring and reducing adverse effects

	Zidovudine	Didanosine	Zalcitabine	Lamivudine	Stavudine
Pyrimethamine	Monitor haematotoxicities				
Quinolones Tetracycline Itraconazole		To absorb 2 h before the ddI			
Ketoconazole		To absorb 2 h before the ddI			Monitor hepatotoxicity
High dose cotrimoxazole	Monitor haematotoxicity			Monitor haematotoxicity	Monitor hepatotoxicity
Sulfadiazine	Monitor haematotoxicity				Monitor hepatotoxicity, neurotoxicity
Dapsone	Monitor haematotoxicity	To absorb 2 h before the ddI Monitor neurotoxicity	Monitor neurotoxicity		Monitor neurotoxicity
Pentamidine IV		Stop ddI	Stop ddC	Monitor amylase levels	Monitor hepatotoxicity amylase levels
Rifampicin					Monitor hepatotoxicity
Isoniazid		Monitor neurotoxicity	Monitor neurotoxicity	Monitor hepatotoxicity	Monitor hepatotoxicity, neurotoxicity
Amphothericin	Monitor haematotoxicity		Monitor nephrotoxicity	Monitor nephrotoxicity	Monitor neurotoxicity

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

(Table 11)

These compounds inhibit the HIV reverse transcriptase by binding to it non-competitively. Because they interact with a specific binding site on the enzyme any slight variation because of a point mutation may cause resistance. Therefore high level resistance develops quickly with this group of compounds if they are not given with other antiretroviral classes. The NNRTIs are inactive against HIV-2. It is currently believed that NNRTIs are only effective when used in 3 drug combinations where each of the other 2 drugs are also new to the patient.

Nevirapine

(Trade name Viramune)

Nevirapine is a dipyrido diazepinone derivative. Synergism has been shown in three drug regimens including zidovudine and lamivudine or didanosine. Nevirapine levels in the cerebrospinal fluid reach 45% of plasma concentrations.

Dosage and administration

Nevirapine can be taken with or between meals.

To evaluate whether a patient might develop an adverse reaction, it is recommended to start with 200 mg orally once a day for 2 weeks. Starting nevirapine at this lower dose supposedly reduces the chance of an adverse event. Then the dosage is increased to 200 mg orally bd.

Adverse effects

Rash, which may be accompanied by fever. Several cases of Stevens-Johnson syndrome have been reported.

Abnormal liver function tests.

Drug interactions

Nevirapine is metabolised via the cytochrome p450. Nevirapine induces cytochrome activity and may therefore decrease, serum levels of protease inhibitors.

The effectiveness of the oral contraceptive pill may be reduced when taking nevirapine.

Rifampicin may decrease nevirapine absorption.

Delavirdine

(Trade name Rescriptor)

Delavirdine is a bis (heteraryl) piperazine derivative. Synergism has been shown with zidovudine, didanosine, zalcitabine or lamivudine.

Dosage and administration

400 mg tds orally.

The drug can be given with or without food. Antacids should not be administered within at least one hour of taking delavirdine.

Adverse effects

Rash (in approximately 40% of patients, usually mild). The rash usually occurs in the first 6 weeks of treatment and will disappear in 2-6 weeks if treatment is continued, however Stevens-Johnson syndrome has been reported. Other side effects include mild headache, nausea, diarrhoea, insomnia, vivid dreams and fatigue.

Abnormal liver function is observed occasionally.

Drug interactions

Delavirdine is an inhibitor of the cytochrome P450 and may therefore increase serum levels of protease inhibitors.

It should not be given at the same time as didanosine (separate administration by at least 1 hour).

Delavirdine increases serum levels of non-sedating antihistamines (terfenadine, astemizole & loratadine) and there is an increased risk of arrhythmias. Many other drugs may decrease absorption of delavirdine including sedative hypnotics (barbiturates), anti-arrhythmics, calcium-channel blockers, ergot-alkaloid preparations, vitamins, H2 antagonists, rifampicin and cisapride.

Antifungals and erithromycin may increase the absorption of delavirdine.

Contraindications/precautions

Do not co-administer with rifampicin, rifabutin, phenytoin, phenobarbital carbamazepine.

Table 11

Non-nucleoside reverse transcriptase inhibitors

Drug Generic (trade) name	Form	Dosage (adults)	Route/conditions	Adverse events	Unit cost in US $	Annual cost in US $
Nevirapine (Viramune®)	T : 100 mg	200 mg qid for 2 weeks followed by 200 mg bid	with or without food	rash abnormal liver tests drug fever	4.12/100mg	6,260
Delavirdine (Rescriptor®)	T : 100 mg	400 mg tid		rash leucopenia abnormal liver tests		

T : tablet

Protease inhibitors

(Tables 12,13,14)

The enzyme protease is responsible for the cleavage of certain viral proteins. This cleavage is needed for the production of new infectious virus particles. The currently approved protease inhibitors bind to the active site of the enzyme. Protease inhibitors are metabolised by the cytochrome P450 system in the liver and many interactions are therefore possible between protease inhibitors and other drugs.

Indinavir

(trade name Crixivan)

Indinavir is a very powerful protease inhibitor. Indinavir has to be taken 3 times daily on an empty stomach. Virus isolates that are resistant to indinavir are generally cross-resistant to ritonavir. Indinavir can be stored at room temperature but in the tightly closed original container of the manufacturer because the capsules are sensitive to moisture.

Dosage and administration

800 mg orally tds. If nevirapine is associated with indinavir the dosage of indinavir should be increased to 1000 mg orally tds. Indinavir has to be taken on an empty stomach, 1 hour before food or at least 2 hours after a meal. If this is difficult - for example when taken in combination with ddI which is taken at a different time of day but also on an empty stomach - indinavir tablets can be taken with a low fat light meal.

Adverse effects

Nephrolithiasis is observed in 1-5 % of the patients. Nephrolithiasis may be a particularly frequent complication in patients treated in warm climates because of insufficient hydration.
Other side effects include : nausea, vomiting, indigestion, diarrhoea, rash, pruritis, dry skin, dry mouth, taste alteration, vivid dreams and lethargy.
Hyperbilirubinaemia occurs frequently but does not cause symptoms. Increased liver enzymes and hyperglycaemia are also seen. A redistribution of subcutaneous body fat has also been noted (lipodystrophy) and a case of coronary artery disease has been described. Delavirdine increases indinavir levels two fold.

Drug interactions

Medications that should not be given with indinavir include rifampicin, astemizole, terfenadine, cisapride, midazolam and triazolam, antifungals and anti-epileptics. Didanosine reduces the absorption of indinavir unless taken > 2 hours apart. Antacids will also decrease absorption of indinavir.

Contraindications/precautions

Precautions when prescribed during the first trimester of pregnancy (informed discussion of the possible risks compared to the benefits). Avoid with severe liver abnormalities. Patients must drink at least one and a half litres of water a day to prevent kidney stones.

Saquinavir

(Trade name Invirase (SQV-HGC) and new formulation Fortovase (SQV-SGC) soft gel capsules)

Saquinavir in its new formulation has increased bioavailability making it a much more effective protease inhibitor.

Dosage and administration

Old preparation saquinavir (SQV-HGC):

The official recommended dosage is 2400 mg tds. Saquinavir should be taken with food.
Saquinavir in this preparation has low bioavailibility. It is now used in association with ritonavir or nelfinavir. (Saquinavir 2 x 400mg ritonavir 2 x 400mg) Taking the capsules with grapefruit juice increases their absorption.

New preparation saquinavir (SQV-SGC):

Has greatly enhanced bioavailability. Soft gel dosage is 1200 mg orally tds, when given as the only protease inhibitor.
When given in combination with nelfinavir 750mg orally tds the saquinavir SGC dosage should be 800 mg orally tds.

Adverse effects
Saquinavir is generally well tolerated. Spontaneous bleeding episodes have been observed in patients with HIV infection with haemophilia. Hyperglycaemia has also been reported.
Minor side effects such as diarrhoea, abdominal pain, headaches, skin rashes and parasthesia may occur.

Drug interactions
Rifampicin reduces saqinavir absorption. Anti-epileptic drugs (phenytoin and carbamazipine) and steroids (dexamethasone) also decrease saquinavir absorption.
Antihistamines such as astemizole and terfenadine should not be given with saquinavir as there is an increased risk of cardiac arrhythmia.
Antifungal drugs (ketoconazole, fluconazole, miconazole, itraconazole) may increase saquinavir absorption.
Hypoglycaemia (with some fatalities) has been reported.

Contraindications/precautions
Saquinavir is contraindicated in people with severe liver test abnormalities.

Ritonavir

(trade name Norvir)
Ritonavir is a very powerful protease inhibitor but has many side effects. When ritonavir is given as the only protease inhibitor in a combination with NRTIs, the optimal treatment dose is 600 mg orally bd. Ideally the drug has to be kept refrigerated at a temperature of 3 - 8 °C. However ritonavir can remain unrefrigerated if kept below 25 °C and used within 30 days.

Dosage and administration
The starting dose is 300 mg orally bd. This dose should be increased progressively over 10-14 days to reach an optimal dose of 600 mg orally bd. Ritonavir has to be taken with food.

Adverse effects
Nausea is very common particularly when starting treatment. Other side effects include vomiting, diarrhoea, anorexia, perioral paresthesias, peripheral paresthesias including a burning sensation of the skin, dizziness, insomnia, changes of taste and tiredness. Some of these side effects are mainly observed during the beginning of the treatment and are dose dependent. They may be avoided to a certain degree by progressively increasing the dose. Other side effects include an increase in serum triglyceride levels (> 200%), uric acid and hepatic enzymes. There is an increased risk of liver toxicity in patients with underlying hepatitis B or C infection. Hyperglycaemia has been reported in patients with and without a known history of diabetes. There are reports of ritonavir causing epilepsy, orthostatic hypotension and renal insufficiency, lipodystrophies and increased bleeding in patients with haemophilia.
As ritonavir may cause dizziness and fatigue it may interfere with some patients' ability to drive.

Drug interactions
Since ritonavir is a very potent inhibitor of the cytochrome P450 system a long list of drugs are contraindicated as concomitant treatment.
Ritonavir increases plasma saquinavir levels 50-100 fold. Therefore the combination of ritonavir 400 mg bd and saquinavir 400 mg bd is useful. This combination is generally well tolerated and the twice daily dosage is an advantage. The most frequently observed side effect is diarrhoea.
Ritonavir reduces the effectiveness of the oral contraceptive pill.

Contraindications/precautions
Severe liver function abnormalities.

Nelfinavir

(trade name Viracept)
Nelfinavir has a good bioavailability and is highly potent. The powder formulation of nelfinavir is being investigated for the treatment of children with HIV infection.

Dosage and administration
750 mg tds. If nevirapine is used in combination with nelfinavir the nelfinavir dosage should be increased to 1000 mg tds.
Nelfinavir has to be taken with food.

Adverse effects

The most commonly reported side effect of nelfinavir is diarrhoea. Other reported side effects include : nausea, elevated transaminase enzymes, hyperglycaemia and lipodystrophy.

Drug interactions
Medications that should not be given with nelfinavir include rifampicin, astemizole, terfenadine and cisapride. Rifabutin levels increase three fold with nelfinavir, so if prescribing together rifabutin levels should be reduced to half. Saquinavir increases nelfinavir levels by about 20%.

Contraindications/precautions
Avoid when patient has severe liver function abnormalities.

Future developments

Once daily preparations
There are several newer and better versions of some of the currently available drugs, which may require less frequent dosing. (For example once daily ddI and twice daily indinavir).

Combined ARVs
Preliminary data shows that the combined formulation produces similar clinical results to the conventional separate drug regimen. It is hoped that combined formulations will make adherence easier. (For example lamivudine (3TC) 150mg + zidovudine (ZDV) 300mg: trade name Combivir)

New drugs
There are currently many new ARVs undergoing clinical trials and under development.

Table 12

Protease inhibitors

Drug Generic (trade) name	Form	Dosage (adults)	Route/conditions	Adverse efffects	Unit cost in US $	Annual Cost in US $
Saquinavir (Invirase â)	C : 200 mg	600 mg tid	with food - high fat preferred	diarrhoea, nausea, abnormal liver tests hyperglycaemia	6.1/600 mg	6,540
Ritonavir (Norvir â)	C : 100 mg S : 1 ml = 80 mg	300 mg bid 3 days 400 mg bid 4 days 500 mg bid 5 days 600 mg bid by day 14	with food	bitter after taste, nausea, vomiting, diarrhoea, circumoral paresthesiasis, polyneuritis abnormal liver tests, triglycerides ↗ hyperglycaemia	11.5/600 mg	8,208
Indinavir (Crixivan â)	C : 200 mg, 400 mg	800 mg tid	1 h. before or 2 h. after a meal (or with a light meal) fluid intake >1.5 l/day	nausea, vomiting, kidney stones polyneuritis abnormal liver tests hyperglycaemia polyneuritis	4.4/800 mg	6,400
Nelfinavir (Viracept â)	T : 250 mg P : 50 mg/g 1 g/scoop	750 mg tid	with food	diarrhoea abnormal liver tests hyperglycaemia		

T : tablet, A : ampoule, S : solution, C : capsule, P : powder

Table 13

Medications that should not be used with protease inhibitors

	Saquinavir	Ritonavir	Indinavir	Nelfinavir	Potential alternatives
Analgesics	-	meperidine piroxicam propoxyphene	-		acetaminophen aspirin oxycodon
Antimycobacterial	rifabutin rifampicin	rifabutin rifampicin	rifampicin	rifampicin	rifabutin clarithromycin ethambutol
Cardiovascular (antiarrhythmic)	-	amiodarone encainide flecainide propafenone quinidine	-		very limited clinical experience
Calcium-channel blocker	-	bepridil	-		very limited clinical experience
Ergot alkaloid (vasoconstrictor)	-	dihydroergotamine ergotamine	-		-
Cold and allergy (antihistamine)	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	loratadine
Gastrointestinal	cisapride	cisapride	cisapride	cisapride	very limited clinical experience
Psychotropic (antidepressant)	-	bupropion	-		fluoxetene desipramine
Psychotropic (neuroleptic)	-	clozapine pimozide	-		very limited clinical experience
Psychotropic (sedative)	midazolam triazolam	clorazepate diazepam estazolam flurazepam midazolam triazolam zolpidem	midazolam triazolam	midazolam triazolam	temazepam lorazepam

Table 14

Important interactions between protease inhibitors (PI) and other drugs (OD)

Saquinavir	Ritonavir	Indinavir	Nelfinavir	Other drug	Effect
	+			**Analgesics**	
	+			meperidine	↗ OD
				propoxyphene	
				fentanyl	
				pyroxicam	pyroxicam
					(gastro intestinal bleeding)
				Antimycobacterials	↘ PI
+	+	+	+	rifampin	↗ rifabutin 4x (Rit*) 2x (Ind*)
	+	+	+	rifabutin	↘ PI
+	+	+	+	**Antifungals**	
				ketoconazole	↗ PI
	+			**Antiarrhythmia**	
				quinidine, amiodarone	↗ OD
				disopyramide	
				lidocaine, mexiletine	
	+			**calcium-channel blocker**	↗ OD
				bepridil	(ventricular arrhythmia)
	+			**Beta blockers**	↗ OD
				metroprolol, pindolol	
				propanolol, timolol	(ventricular arrhythmia)
	+	+	+	**Anticonvulsants**	↘ PI, ↗ OD (↓ phenytoin)
				carbamazepine	
				clonazepam,	
				phenytoin, phenobarbital	
	+			**Anticoagulant**	↗ warfarin
				warfarin	

* Rit = Ritonavir
* Ind = Indinavir

	+			**Ergot alkaloid (vasoconstrictor)** ergotamine dihydroergotamine	↗ OD
	+		+	**Cold and allergy (antihistamine)** astemizole, terfenadine	↗ OD (ventricular arrhythmia)
	+		+	**Cold and allergy (antihistamine)** astemizole, terfenadine	↗ OD (ventricular arrhythmia)
	+			**Theophylline**	↘ theophylline (43%)
	+	+	+	**Gastrointestinal** cisapride	↗ cisapride (cardiac arrhythmia)
	+ +			**Antiparasites** quinine mefloquine	↗ quinine ↗ mefloquine
	+			**Psychotropic (antidepressant)** bupropion	↗ bupropion (seizures)
	+			**Psychotropic (neuroleptics)** clozapine	↗ clozapine (agranulocytosis, seizures)
 +	+ +	+ +	+ +	**Psychotropic (sedative)** diazepam triazolam	↗ OD
	+	+	+	**Anticonvulsants** carbamazepine clonazepam, fenytoin, phenobarbital	↘ PI, ↗ OD (↓ fenytoin)
	+		+	**Oral contraceptives** (ethinyl estradiol)	↘ ethinyl estradiol (40%)
+		+		**Grapefruit juice**	↘ Indinavir↗Saquinavir
	+			**metamphetamine** **"Ecstasy"**	↗ OD

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme
on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

Office of AIDS and Sexually Transmitted
Diseases (ASD)
World Health Organization
20 Ave Appia
CH-1211 Geneva 27
Tel: 41 22 791 4613
Fax: 41 22 791 4834

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Guidance Modules on Antiretroviral Treatments

Module 5
Laboratory Requirements for the Safe and Effective Use of Antiretrovirals

Joint United Nations Programme on HIV/AIDS (UNAIDS)

World Health Organization (WHO)

WHO/ASD/98.1
UNAIDS/98.7

Acknowledgements

The World Health Organization and UNAIDS would like to thank Professor Gunnel Biberfeld, Swedish Institute for Infectious Disease Control, Stockholm, Sweden, for preparing the text of this module;

Dr Gaby Vercauteren, Blood Safety Unit, WHO, Dr Frank De Wolf, University of Amsterdam, the Netherlands and Professor Nkandu Luo, University Teaching Hospital, Lusaka, Zambia, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for coordinating the project.

Module 5
Laboratory Requirements for the Safe and Effective Use of Antiretrovirals

Introduction

The introduction of combination antiretroviral treatment (ARV) for HIV infection has dramatically changed the clinical perspective for people living with HIV/AIDS, for health care professionals responsible for their care and for policy makers. This module reviews the laboratory requirements for safe and effective use of ARVs including:

- Diagnosis of HIV infection through the detection of antibodies or viral genome by polymerase chain reaction (PCR)
- Monitoring of adverse reactions to ARV drugs
- Diagnosis of opportunistic infections
- CD4+ T-cell determinations
- Viral load monitoring
- Monitoring of resistance of HIV

The importance of reliable and accurate laboratory support for ARV treatment is stressed and basic information provided on how to achieve a high standard of performance. Well trained staff is a prerequisite for a high standard of performance. Basic training and regular refresher training should be routine in the laboratories set up for ARV services. Cost estimates provided are based on commercial prices given by the manufacturers. Costs may vary between geographical areas and are often negotiable. Labour costs have not been included.

HIV testing

The standard procedure for laboratory diagnosis of infection with the human immunodeficiency virus (HIV) usually includes screening for virus specific antibodies with an enzyme-linked immunosorbent assay (ELISA) or a rapid simple test, followed by confirmatory testing of screened positive samples[1].

The most widely used screening tests are ELISAs which comprise a number of variants based on different principles including indirect, competitive, sandwich and capture assays, all of which may detect HIV-1 as well as HIV-2 antibodies. Most of the first generation ELISA tests were based on viral lysate antigens. Later variants utilise recombinant proteins and/or synthetic peptides. The latter are generally more sensitive and specific as there are fewer contaminating products such as cellular components in the viral lysate. Through a WHO initiative, extensive evaluations of HIV antibody assays have been performed.

The antibody screening assays, though very sensitive, specific and reproducible, are not completely free from false reactions. The most common testing strategy for detection of HIV

[1] Joint United Nations Programme on HIV/AIDS (UNAIDS)/WHO. Revised recommendations for the selection and use of HIV antibody tests. Weekly Epidemiological Record 1997;72:81-88.

antibodies is therefore to perform a second more specific supplementary (confirmatory) assay on sera repeatedly reactive on a screening assay. Western blot (WB) and/or line immunoassays (LIA, RIBA) are tests used specifically for serological confirmation.

WB tests are expensive, time consuming and have technical disadvantages, such as lack of standardisation in performance and interpretation, and indeterminate reactions. Therefore, alternative strategies for confirmation of HIV antibody positive samples that can replace conventional WB testing have been evaluated. WHO has issued guidelines on testing strategies according to the purpose of testing. The general principle is to use a combination of cheaper and less sophisticated tests, e.g. two or three ELISAs or simple/rapid tests, in such a way that sensitivity and specificity will be comparable to the more commonly used strategies including confirmation by WB. Ideally, an alternative strategy for confirmation of HIV infection should consist of a combination of assays of different test principles and different antigen preparations. It is also possible to design an alternative strategy for confirmation to include discrimination between HIV-1 and HIV-2. Furthermore, the complete test procedure (from receiving the sample to sending out the final result), using the alternative confirmatory strategy, saves time. Positive samples may be confirmed and results submitted to the referring doctors the same day as they have been screened.

Apart from standard laboratory equipment, ELISA testing requires a spectrophotometer at a cost of around US$ 10,000. Simple/rapid test kits are often supplied with all the reagents needed while basic utensils such as serum tubes, pipettes and a simple centrifuge for separation of serum have to be provided by the laboratory. For storage of test kits a refrigerator is required. Serum can be kept in a refrigerator for some time but for longer storage they should be frozen at -20^{O}C at least. ELISA tests for HIV can be purchased from around US$1 per test, while simple/rapid tests are usually more expensive (from around US$3). Western blot tests cost US$ 20 - 30. Many HIV antibody tests can be obtained through WHO bulk purchase at a reduced rate.

Apart from HIV antibody measurements, detection of virus genome by nucleic acid amplification techniques (NAT), such as the polymerase chain reaction (PCR) has a place in certain cases for confirmation of HIV infection. NAT are particularly useful for further characterisation of virus strains, such as subtyping, monitoring of resistance to ARV drugs, and measurement of viral load. PCR is also the main mode of diagnosis of HIV in infants. In settings with limited laboratory facilities, modified heat-denatured antigen detection may be used as an alternative to PCR for the early diagnosis of HIV infection in infants. While antigen detection is mainly based on the same principles as antibody testing, NAT are sensitive and complicated methods requiring special laboratory facilities, instruments and skills, and careful quality assurance. For further information on PCR and related NAT, see the sections on viral load monitoring and monitoring resistance of HIV.

Finally, it should be noted that when HIV infection has been detected for the first time in a person, the diagnosis should always be reconfirmed on a second blood sample, in order to exclude laboratory and administrative mistakes.
In conclusion, laboratory diagnosis of HIV infection is usually in the initial phase done by the detection of HIV specific antibodies in serum or plasma. Antibody detection can be done with simple/rapid tests which require a minimum of laboratory equipment and material.

Testing strategies based on simple/rapid assays are most suitable for small numbers of specimens. For larger numbers of specimens it is more practical and economic to use ELISAs. These assays require larger investments in equipment and a regular supply of electricity and water. Detection of the virus itself, through antigen detection or NAT is usually used for specific purposes, e.g. during early stages of infection when antibody levels may be low, for diagnosis in infants born to mothers with HIV,for subtyping of virus strains, or for determination of virus load.

Monitoring of patients for adverse reactions to ARVs

Like most potent medical drugs, ARVs may cause adverse reactions which have to be weighed against the potential benefits. Adverse reactions vary from one drug to another and between individual patients. Some are of a general character and can be monitored clinically, e.g. skin rashes, nausea, headache and polyneuropathy. Some adverse reactions decline after time. Other adverse reactions can be monitored with laboratory tests. The major ARV drugs, their most important side effects and the modes of detection and follow-up of these adverse reactions are summarised in Table 1.

Among nucleoside reverse transcriptase inhibitors (NRTIs), zidovudine may cause anaemia and neutropenia. Lamivudine has relatively few side effects while the other NRT inhibitors have caused pancreatitis in a few cases. Thus, regular blood counts and analyses of amylase in serum (or symptomatic patients) are required. Among the protease inhibitors, indinavir may cause elevated bilirubin levels and clinical nephrolithiasis with pain in the flank and hematuria (reported in 3-5% of all patients). The most common adverse events reported for the other protease inhibitors are diarrhoea and other gastrointestinal disturbances. Protease inhibitors have also been reported to cause liver enzyme elevations and diabetes mellitus in a few cases.

Timing of check-ups depends on the status of the patient. If the patient tolerates the treatment well and is in a stable clinical condition, the interval between check-ups can be extended to 3-4 months. Otherwise the intervals should be shorter according to need, as decided by the doctor in charge.

In conclusion, regular clinical and laboratory monitoring of patients on ARVs is necessary. The laboratory tests to be performed depend on which ARV drugs are being used, but generally comprise blood counts including differential, as well as bilirubin and liver enzymes, amylase, urate and glucose (simple dip tests of the urine are usually sufficient). It must be emphasised that baseline laboratory analyses should be performed before ARV treatment is started.

Table 1: Antiretroviral drugs, main adverse reactions and follow-up action/tests

Drug	Adverse reactions	Follow-up action/tests
1. **Nucleoside Reverse Transcriptase Inhibitors**		
1.1. Zidovudine (ZDV, 3^1-azido-2^1, 3^1-dideoxythymidine)	- initial headache and nausea (usually temporary) - anaemia, leucopenia (neutropenia) - myopathy	- clinical examination - blood count including differential - CK
1.2. Didanosine (ddI, 2^1, 3^1-dideoxyinosine)	- gastrointestinal disturbances - polyneuropathy (long term treatment) - pancreatitis	- clinical examination - clinical examination - amylase
1.3. Lamivudine (3TC)	(few)	
1.4. Zalcitabine (ddC, 2^1, 3^1 - dideoxycytidine)	- polyneuropathy - ulcerative stomatitis - pancreatitis	- clinical examination - clinical examination - amylase
1.5. Stavudin (d4T, 2^1,3^1 - didehydro-dideoxy-thymidine)	- peripheral polyneuropathy (common) - abnormal liver function tests (LFT) - pancreatitis (rare)	- clinical examination - liver enzymes - amylase
2. **Non-nucleoside Reverse Transcriptase Inhibitors**		
2.1. Nevirapine	- skin rash (common) - elevation of liver enzymes	- clinical examination - liver enzymes
2.2. Delavirdine	- skin rash (common) - abnormal LFT	- clinical examination - liver enzymes
3. **Protease Inhibitors**		

3.1. Indinavir	- nausea, gastrointestinal disturbances, headache, dry skin - elevation of bilirubin - kidney stones/flank pain - diabetes mellitus (rare) - haemolytic anaemia (rare) - liver dysfunction (rare)	- clinical examination - bilirubin - urinary dip tests (glucose, erythrocytes) - bilirubin, liver enzymes
3.2. Ritonavir	- nausea, gastrointestinal disturbances - paresthesias - elevation of serum levels of liver enzymes, urate, glutamyl-transpeptidase (GT), creatine-kinase (CK), triglycerides - diabetes mellitus (rare)	- clinical examination - clinical examination - analysis of serum levels of: liver enzymes, urate, GT, CK, triglyceride - analysis of glucose in urine
3.3.Nelfinavir	-gastrointestinal disturbances (around 20 % of patients) - hyperglycaemia and lipodystrophy.	- clinical examination - analysis of glucose in urine - liver enzymes

IDENTIFICATION AND DIAGNOSIS OF OPPORTUNISTIC INFECTIONS

Opportunistic infections are significant clinical features of HIV/AIDS and their detection and treatment is of considerable importance in the care of HIV infected people. The incidence of opportunistic infections usually decreases with the introduction of ARVs. However, in cases of non-optimal compliance with ARV treatment or the development of resistance to the ARV drugs used, opportunistic infections may reappear.

A summary of the main opportunistic infections and complicating syndromes in HIV disease including the mode of diagnosis and basic equipment and reagents needed, is provided in Table 2. (For further reading see Reference 9.)

Some of the opportunistic infections, like oral or oesophageal candidiasis, cytomegalovirus retinitis and cutaneous Kaposi's sarcoma (KS) may require only a clinical examination for diagnosis and follow-up (KS is often confirmed by histopathological examination of tissue specimens). Many of the parasitic infections can be diagnosed by microscopy of relevant specimens, such as stool and tissue preparations. Lymphomas will also be diagnosed and typed through histopathological examination by microscopy of tissue specimens. A pulmonary X-ray in combination with microscopy of a sputum sample is often sufficient for confirmation of pulmonary tuberculosis or pneumocystis carinii infection. Computed tomography (CT) or magnetic resonance imaging (MRI) are valuable tools in the of brain

manifestations of HIV disease, such as toxoplasmosis of the brain, lymphomas and progressive multifocal leukoencephalopathy (PML). For proper confirmation of bacterial infections it is necessary to perform cultures. Tuberculosis and virus cultures require special laboratory facilities and reagents.

Thus, with a good knowledge and clinical experience, it is possible to adequately monitor many opportunistic infections with clinical examinations and basic technical facilities, such as light microscopy and chest X-ray only. Diagnostic possibilities can be extended with the addition of a bacteriological laboratory. Ideally, facilities for TB and virus cultures, CT and/or MRI scans should be available. The level of sophistication will be determined locally according to needs, available resources and existing technical facilities.

Table 2. Summary of main opportunistic infections and complicating syndromes in HIV infection, mode of diagnosis, basic equipment and reagents

Disease	Frequency [c]	Mode of diagnosis	Equipment and reagents	Priority [b]
1. Protozoan Infections				
1.1. Pneumocystis carinii	***	- clinical examination [a]		*
		- microscopy of sputum (if possible, induced sputum)	- light microscope, staining material	*
		- pulmonary X-ray	- X-ray equipment - film and reagents for film processing	*
		- bronchoscopy (e.g. with BAL)	- bronchoscopy equipment (for BAL also light microscope and staining material	
1.2 Toxoplasmosis	**	- clinical examination		*
		- detection of serum antibodies	- see text, section....	*
		- CT	- CT equipment	(*)
		- MRI	- MRI equipment	
		- brain biopsy histology (exceptional)	- (surgery), light micro-scope, staining material	
1.3. Cryptosporidiasis	*	- stool microscopy	- light microscope	*
1.4. Isospora belli	*	- stool microscopy	- light microscope	*
2. Bacterial infections				
2.1. Tuberculosis (TB)	***	- clinical examination		*
		- microscopy of sputum	- light microscope, acid-fast stain	*
		- pulmonary X-ray	- see 1.1	*

		- culture	- TB laboratory facilities	
2.2. Mycobacterium avium complex	*	- culture	- see 2.1	*
2.3. Bacterial pneumonia	**	- clinical examination - pulmonary X-ray - culture (nasopharyngeal, sputum or blood)	 - see 1.1 - standard bacteriological laboratory facilities	* *
2.4. Bacterial gastroenteritis	**	- clinical examination - culture (stool) - stool microscopy (for exclusion of parasitic infections)	 - see 2.3 - light microscope	*

Disease	**Frequency [c]**	**Mode of diagnosis**	**Equipment and reagents**	**Priority [b]**
3. Viral Infections				
3.1.Cytomegalovirus CMV) Ocular infection	*	- clinical examination - ophthamological examination	- ophthalmoscope - (ophthalmological micro-scope)	*
central nervous system infection		- PCR of CSF	- PCR equipment see text, section.....	(*)
gastrointestinal infection		- endoscopy with biopsy - histopathological examination of biopsy material	- endoscopy equipment (rectoscope) - light microscope, staining material	* *
3.2. Varicella zoster virus (VZV)	*	- clinical examination - antigen detection by immunofluorescence (IF) - viral culture	 - immunofluorescence microscope, reagents - virological laboratory facilities	*

3.3. Herpes simplex virus (HSV)	**	- clinical examination - IF - antibody detection - histopathologic examination of biopsy material - PCR - viral culture	 - see 3.2 - see 1.2 - see 3.1 - see 3.1 - see 1.2	* (*)
3.4. Progressive multifocal leucoencephalopathy (PML)	*	- clinical examination - PCR of CSF (JC virus) - CT - MRI - brain biopsy histology (exceptional)	 - see 1.2 - see 1.2 - see 1.2 - see 3.1	* * (*)
4. Fungal infections				
4.1. Candida	***	- clinical examination - microscopy of plaque scrapings - endoscopy - X-ray (e.g. oesophagus)	 - light microscope - see 3.1 - see 1.1	* (*) (*) (*)

Disease	Frequency	Mode of diagnosis	Equipment and reagents	Priority
4.2. Cryptococcus neoformans	**	- serum antigen detection	- see 1.2	(*)
		- CSF antigen		(*)
		- culture	- laboratory facilities for mycological cultures	
		- histopathological examination of biopsy material	- mucicarmine stain, India ink stain	
4.3. Histoplasma capsulatum	*	- serum antigen detection	- see 1.2	(*)
		- histo- or cytopathological examination of biopsy material, sputum or lavage specimens	- see 3.1	
		- culture	- see 4.2	
4.4. Coccidioides immitis	*	- serum antigen detection	- see 1.2	(*)
		- histopathological examination of biopsy material	- see 3.1	
		- culture	- see 4.2	
5. Other diseases				
5.1. Kaposi's sarcoma	**	- clinical examination		*
		- histopathologic examination of biopsy material	- see 3.1	

5.2. Lymphomas	*	- clinical examination - cyto- or histopatho- logical examination of biopsy or cell material - Ultrasonography - CT - MRI	 - see 3.1 - Equipment for ultrasonography - see 1.2 - see 1.2	
5.3 HIV wasting syndrome	**	- clinical examination		*
5.4 Other HIV related neurological compli- cations	*	- clinical examination		*

a) Clinical examination also includes clinical history and, ideally, routine blood samples such as full blood counts and inflammatory parameters.

b)* Minimum (basic) requirement

(*) Additional requirement

c) *** common
** less common
* rare
(N.B. May vary by geographical region or population group)

BAL, Bronchoalveolar lavage

CT, Computed Tomography

MRI, Magnetic Resonance Imaging

PCR, Polymerase Chain Reaction

CSF, Cerebrospinal fluid

DETERMINATION OF CD4+ T-CELL COUNTS

Determination of CD4+ T-cell counts has for many years been the conventional method for assessing the immune status of HIV infected persons. Low levels of CD4+ T-cells (<200 cells/cmm) predict decreased survival and increased risk of acquiring opportunistic infections. More recently the introduction of methods for assessment of plasma viral RNA levels has provided an alternative and complement to CD4+ T-cell measurements. Since

plasma viral load is also a good predictor of clinical progression of the HIV disease, the need for regular CD4+ T-cell measurements may decrease. However, determination of CD4+ T-cell counts is still widely used, often in parallel with plasma viral load determinations. The extent to which CD4+ T-cell counts and plasma viral load measurements should be used and how the two methods can complement each other, is still to be determined.

In industrialised countries, the standard method for performing CD4+ T-cell counts in HIV-infected people is by flow cytometry. The method for flow cytometric immunophenotyping of peripheral blood samples using two-, three-, or four-colour monoclonal antibody panels is highly standardised and results are generally accurate and reliable. Most laboratories measure absolute CD4+ counts combining the results of two (or three) different laboratory techniques: the proportion of CD4+ T-lymphocytes is determined by flow cytometric analysis whereas the lymphocyte count (or the white blood cell count and the differential) is measured by haematological testing. Thus, each of the techniques used contributes to the accuracy of the final results.

Recently, several methods have been developed to derive absolute CD4+ T-cell counts directly from flow cytometric analysis. Such methods may yield less variable results but the accuracy must be validated against the laboratory's currently used conventional method. Laboratories performing CD4+ T-cell counts should follow published guidelines as well as manufacturers' instructions, and participate in performance evaluation programmes (11).

Flow cytometric instruments can today be purchased from three different manufacturers at a cost of around US$ 40,000 - 80,000. These instruments require highly trained personnel and are thus unsuitable for routine use in laboratories with limited facilities. In such places, specimens may be transported to a central laboratory if they can be maintained at room temperature during transport and if they can be processed within acceptable time limits. A specimen for flow cytometric immunophenotyping must be processed within 48 hours of sample collection. Haematological testing must be performed within the time limit for which the haematology instrument has been validated, usually varying from less than 6 to 30 hours after specimen collection. Immunophenotyping and haematological testing can thus be carried out at different laboratories. If specimens cannot be transported to laboratories at required temperatures or within acceptable time limits for flow cytometric analysis, e g in developing countries, an alternative method for CD4+ T-cell enumeration may be used.

Alternative methods for monitoring CD4+/CD8+ T-lymphocytes are summarised in Table 3. Alternative assays were reviewed in a WHO workshop in 1992. Results of a WHO collaborative multicentre field evaluation of alternative CD4 quantification techniques and other studies have demonstrated the reliability of these techniques and their potential for use in settings with limited facilities. A variety of assay principles exist, including commercial kits as well as in-house systems based on immunological reagents also available commercially. Some assays are designed to detect $CD4^+$ cells only whereas others also detect $CD3^+$ and $CD8^+$ cells. The various assay principles include detection of lymphocytes through labelling with monoclonal antibodies (mab) and then visualisation by colour reagents, either directly conjugated to the MAB (FACScount, Cytosphere, the immunoalkaline phosphatase technique) or indirectly via lysis of the mab labelled cells (Dynabeads). In the latter case the cells are visualised by trypan blue staining of the cell

nuclei remaining after lysis. Alternatively, the CD4 and/or CD8 molecules may be detected by ELISA techniques, either directly on the cells (Capcellia, Zymmune) or after releasing of the cell surface molecules through solubilization treatment (TRAx CD4). Apart from FACSCount, which requires a special instrument, these techniques can be applied without sophisticated instrumentation; Cytosphere, Dynabeads and the immunoalkaline phosphatase technique are read in a light microscope while Capcellia, Zymmune and TRAx CD4 require instruments for ELISA analysis. The correlation between the alternative methods and flow cytometry is generally high, although in some studies variable correlation coefficients have been observed particularly for the ELISA based techniques when testing African samples (Table 1). When comparing the various methods with flow cytometry the correlation coefficients may be high but the values obtained may be consistently too low or too high. It is, thus, important to evaluate and standardise the method chosen, in the local environment.

The choice of method will vary from one setting to another since each meets different laboratory requirements (Table 3). For example, methods based on the microtitre enzyme immunoassay technique would be suitable for laboratories which handle a large number of specimens but which have few staff. Such assays are also suitable for specimens collected from remote sites since they allow samples to be frozen and shipped in batches for testing. Methods based on cell counting using a microscope would be of use in laboratories which process few samples and have few staff. In general, the alternative methods require lower initial investments and are cheaper to perform than conventional flow cytometry. The price of the reagents needed to test one sample using an alternative method is about US$ 5-10, with the exception of FACSCount and Capcellia which are more expensive. The corresponding cost using a flow cytometric method is US$ 10-15. However, the alternative assays are less flexible and often more time consuming which is a constraint in large scale investigations.

When using the alternative methods for follow-up of patients it should be noted that results are likely to be more consistent if the same method is used each time. It is therefore recommended that laboratories use one type of assay. If a change is necessary it should be evaluated locally in parallel with the previous assay in order to make correct comparisons of the results over time. Quality control programmes should also be set up and form part of the assay protocol.

In conclusion, the conventional and most reliable method for accurate CD4+ T-cell counts, especially when carried out large-scale, is flow cytometry. If flow cytometric analysis is not available, a number of alternative methods are available. These alternative methods meet different laboratory requirements and suit different settings. The initial investment and the cost of maintenance of equipment are substantially higher for flow cytometry testing as compared to alternative methods. These costs and subsequent expenditures for reagents for each tested sample are thus dependent on what method is used but do not vary much between different countries. Requirements for trained personnel and labour intensity largely depend on the method and thus, the labour costs will vary between different countries. The accuracy of the assay used has to be monitored and this is especially important when an alternative method is chosen.

Table 3. **Summary of main characteristics of seven alternative methods for CD4/CD8 lymphocyte determination and flow cytometry.**

	Flow cytometry	**FACSCount ™**	**Cytosphere**	**TRAx™CD4**	**Zymmune**	**Dynabeads®**	**Capcellia**	**Immunoalkaline Phosphatase**
Manufacturer	Becton Dickinson Coulter Corp. Ortho Diagnostic Systems	Becton Dickinson	Coulter Corp.	T Cell Diagnostics	Zynaxis Inc	Dynal A/S	Sanofi Diagnostics Pasteur	In-house assay with commercially available reagents
Instrument	Flow cytometer and computer assisted analysis. Preparation can be automated. May need use of cell counter.	Automated special instrument	Automated or light microscope and hemato-cytometer	Microtiter EIA	Microtiter EIA	Magnetic particles and counting equipment* or light microscope	Microtiter EIA	Light microscope
Detection system	Fluorescence labelled MAB against cell surface molecules	Fluorescence labelled anti-CD3, CD4 and CD8 MAB	Beads conjugated to anti- CD4 MAB	anti-CD4 and CD8 MAB	anti-CD4 and CD8 MAB	Magnetic beads conjugated to anti-CD4 and CD8 MAB	anti-CD4 and CD8 MAB	Slide based staining with anti-CD3, CD4 and CD8 MAB
Specimen	Whole blood with RBC lysis	Whole blood	Whole blood	Whole blood	Whole Blood	Whole blood	PBMC	Blood smear

Results	Double, triple or quadruple stainings of any cell surface marker where MAB are available	CD3, CD4 CD8 counts	CD4 counts	CD4 cell no. equivalent	CD4 and CD8 counts	CD4 and CD8 counts	pmol CD4/L and CD8/L	CD3, CD4, CD8 counts
Precision (Coeff variation)	< 5 > 15 % (depending on method used)	4 %	<5 %	<8 %	5 %		<10 %	95 % CI ±8-14
Correlation with flow cytometry (Correlation coeff)	NA	0.93-0.98 (several international studies)	0.74-0.91 (several international studies)	0.63-0.91 (several international studies)	0.92-0.94 (two studies in USA)	0.94 (one study only)		0.96 (one study only)
Cost (instruments, USD)	40 - 80 000	20 000	2 000	15 000	15 000	2 000	15 000	2 000
Cost/test (reagents only; USD; approx.)	10-15	20	8	6		5	28	3

Advantages	Powerful and flexible Allows for double, triple or quadruple stainings Can be used for examination of difficult samples where alternative techniques often are insufficient	Few steps, less human error Low biohazard risk Quick results Gives CD3, CD4 and CD8 counts	Simple and rapid	Simple Long sample shelf life Can process many samples at a time	Simple Can process many samples at a time Gives CD4 and CD8 counts	Simple and rapid Gives CD4 and CD8 counts Flexibility in counting Small sample volume	Gives CD4 and CD8 counts	Low cost Long specimen shelf life Small sample volume
Disadvantages	Expensive equipment and reagents Complex, requires highly trained personnel	Expensive equipment and reagents Work station allows only 8 samples at a time	Short shelf life Gives only CD4 counts	Pipetting viscous samples difficult Gives CD4 counts only	Many pipetting steps	Few samples processed at a time. Subjectivity in visual counting. Short specimen shelf life. Not available as a kit	PBMC isolation by density centrifugation Expensive	Laborious manual counting Complicated staining process Not available as a kit

***) Automated cell counter or hematocytometer; PBMC - Peripheral blood mononuclear cells; Mab - Monoclonal antibodies; EIA - Enzyme immunoassay; CI - Confidence interval; RBC - Red blood cells; NA - Not applicable.**

VIRAL LOAD MONITORING

Background

Our understanding of the pathogenesis of AIDS has greatly benefited from two recent therapeutic and methodological breakthroughs, namely the development and use of highly active antiretroviral combination therapy and the quantification of HIV-1 viral RNA in plasma. It has been shown that plasma levels of virus decrease very rapidly after the initiation of antiretroviral treatment. Typically, plasma HIV-1 RNA levels fall around 2 logs in the first two weeks of treatment. This rapid decline is followed by a slower second phase of decline.

Quantification of human immunodeficiency virus type 1 (HIV-1) RNA in plasma has rapidly become a widely used method for follow-up of HIV-1 infected individuals. It is considered a crucial element of clinical management for assessing prognosis and effectiveness of therapy. This is based on the fact that plasma HIV-1 RNA levels appear to reach a set-point shortly after primary infection and that this set-point level strongly correlates with the subsequent risk of clinical progression. Moreover, early changes in RNA levels in response to treatment appear to predict long-term clinical benefit. In industrialised countries, the large scale use of quantitative HIV-1 RNA measurements has been greatly facilitated by the development of standardised, commercial kits.

Available methods

At present three commercial assays are available for the quantification of HIV-1 RNA in plasma, namely the HIV monitor assay (Roche), the Nuclisens HIV-1 QT (NASBA, Organon) and the Quantiplex HIV-RNA assay (bDNA, Chiron). The main characteristics of these assays are summarised in Table 4. These assays are under continuous development and new protocols which enable quantification down to around 50 copies of RNA per ml plasma and better detection of all genetic subtypes of HIV are currently being distributed. The cost per test (from the three companies) is officially a little less than US$100. In-house methods for quantification of HIV-1 RNA have been described, but cannot be generally recommended mainly because within and between run variation is difficult to assess. A new improved method for quantification of HIV-1 p24 antigen in plasma exists but this assay has not yet been as extensively evaluated as the RNA assays. However, it holds potential for a less costly alternative in settings with limited resources.

HIV monitor (Roche)

The HIV monitor assay is based on the polymerase chain reaction (PCR) technique. Viral RNA is extracted from 200 µl of plasma and following reverse transcription PCR the HIV-1 RNA copy numbers are determined by an ELISA-like method. The assay takes approximately 8 hours to run. The lower limit of detection is 200-500 HIV-1 RNA copies per ml plasma, but a modified assay with a lower limit of detection (50 copies per ml) is being developed. This modified assay requires ultracentrifugation of 500 µl plasma prior to RNA extraction. The first (current) version of the assay gives false low results with samples from many subtype A and E infected persons, but new versions (add-in primer and version 1.5) of the assay with improved detection of HIV-1 group M subtypes are becoming available. However, HIV-1 group O and HIV-2 are not detected. Equipment includes a thermocycler (cost approximately US$10,000) an ELISA photometer (cost approximately US$15,000) and for the ultrasensitive technique, an ultracentrifuge (cost approximately US$25,000).

Nuclisens HIV-1 QT; NASBA (Organon)

The Nuclisens HIV-1 QT is based on the NASBA (nucleic acid sequence based amplification) method, which is an isothermic amplification method which uses three enzymes (reverse transcriptase, RNase H and T7 RNA polymerase). The viral RNA extracted from plasma is NASBA amplified and the detection system is based on electrochemoluminescence (ECL) which requires a special apparatus. The assay takes approximately 12 hours to run. The lower limit of accurate quantification is dependent on the sample volume used, with 200 µl of plasma input the detection limit is 400 copies/ml. However, up to 2 ml plasma can be used resulting in a detection limit of 40 RNA copies/ml plasma. The first (current) version of the assay gives false low results with samples from many subtype A and E infected people. HIV-1 group O and HIV-2 is not detected. Equipment required includes a heat-block (cost approximately US$3,000) and special detection apparatus (Table 4).

Quantiplex HIV-RNA assay; bDNA (Chiron)

The bDNA assay differs from the other two assays in that it is based on signal amplification rather than target amplification. The assay has an ELISA like format. Virus is concentrated from 1 ml of plasma by ultracentrifugation and viral RNA is released in a buffer which contains multiple HIV-1 probes. The HIV-1 RNA (with attached probes) is allowed to bind to microplate wells coated with HIV-1 specific capture probes. Enzyme labelled detection probes (branched DNA) and a chemiluminescent substrate are subsequently added and the light output is measured in a special chemoluminescensometer. The assay takes approximately two days to run. The lower limit of accurate quantification is 500 copies/ml and around 100 copies/ml in a revised assay. The assay appears to be able to detect all genetic subtypes within group M with equal efficiency. HIV-1 group O and HIV-2 are not detected. Equipment required includes an ultracentrifuge (cost approximately US$25,000), and the special detection apparatus (Table 4).

Comparison of the methods

The three commercially available assays are very similar in terms of cost, labour, sensitivity and precision. Thus, no single assay can be considered superior. There are, however, small differences between the assays which may be important in some situations. The equipment needed for the Roche assay is often already at hand in the laboratory, but the special apparatus needed for the other two assays can probably be obtained for free or at low cost from the manufacturers, at least if large sample series are analysed. Furthermore, the more extensive special set-up for the Organon and Chiron assays makes them more suitable for large scale analysis. The somewhat longer time required to complete the Organon and Chiron assays is mainly due to longer incubation times. In most countries, except possibly the USA, many genetic subtypes coexist; thus, assays which do not detect all subtypes with equal efficiency, i.e. the first generation Roche and Organon assays, should probably be avoided.

It should be noted that for all three assays computer equipment is also required.

Options for different settings

There are really only two options: to use or not to use HIV-1 RNA assays for routine monitoring of HIV-1 infected individuals. The cost of the assays, equipment and a suitable laboratory facility are the major obstacles. In addition, well trained technicians are a prerequisite for a meticulous and accurate use of the assays. However, in relation to the cost of modern antiretroviral combination therapy with protease inhibitors, the cost of HIV-1 RNA quantification is moderate. It can be argued that RNA quantification should be used in settings where combination therapy is given. It is likely that monitoring of HIV-1 RNA levels before and during treatment will be cost-effective, because it will give information about when treatment should be started, stopped or changed. Recommendations

about how HIV-1 RNA levels should be used in routine patient care have been published. In untreated patients HIV-1 RNA levels are usually measured every four to six months. After start of treatment, measurements are usually performed every three months and often also one month after start or change of treatment.

Table 4. Summary of main characteristics of assays for viral load monitoring

Method	Principle	Detection limit	Comments	Special equipment needed	Cost (US$)
HIV Monitor (Roche)	RT-PCR followed by ELISA-like method to determine copy numbers	Standard: 200-500 HIV-1 RNA copies/ml plasma Ultrasensitive: 50 copies/ml	Equipment often available for other purposes, in standard virological laboratories First generation assay gives false low results with many subtype A and E samples HIV-1 group O and HIV-2 are not detected	- thermocycler - ELISA photometer - ultracentrifuge	10 000 15 000 25 000
Nuclisens HIV-1 QT; NASBA (Organon)	Isothermic amplification of extracted RNA, using three enzymes (NASBA). Electrochemoluminescence (ECL) based detection system	Standard: (sample volume 2(µl): 400 HIV-1 RNA copies/ml plasma Using 2 ml plasma: 40 copies/ml	First generation assay gives false low results with many subtype A and E samples Special detection apparatus needed HIV-1 group O and HIV-2 are not detected	- special detection apparatus - heat block	negotiable 3 000

Quantiplex HIV-RNA assay; bDNA (Chiron)	Signal amplification through enzyme labelled detection probes. Chemoluminescence based detecti system	Standard: 500 HIV-1 RNA copies per ml plasma Revised: 100 copies/ml	Detects all HIV-1 group M strains Does not detect HIV-1 group O or HIV-2. Special detection apparatus needed	- Ultracentrifuge Special detection apparatus (chemoluminescenso eter)	25 000 negotiable

MONITORING OF RESISTANCE OF HIV

Background

HIV is characterised by a high level of genetic variability and rapid evolution which gives it an extraordinary ability to respond to environmental changes such as that induced by antiretroviral therapy. As a consequence development of resistance is the major obstacle to long-term effective treatment.

Resistant virus variants have been documented to virtually all antiretroviral drugs which are in use or under development. Resistance can develop within weeks after onset of treatment with single antiretroviral drugs, such as the non-nucleoside reverse transcriptase inhibitors (NNRTI) and 3TC, because of the rapid turn-over of HIV-1 *in vivo*. The speed with which resistance develops is in part determined by the number of mutations required for full resistance. For some drugs, such as those mentioned above, a single point mutation is sufficient for complete resistance. In such cases resistant variants are usually present, albeit at low level, within the pre-treatment virus population. Resistance to other drugs or drug combinations require multiple mutations. Such variants do not usually pre-exist, but instead evolve as the virus consecutively acquires more and more mutations. To avoid development of resistance it is important to use drugs which cannot be circumvented by single mutations and which are potent enough to block virus replication and thereby the risk of accumulation of mutations. These two goals can in principle only be achieved by simultaneous use of three or more drugs, i.e. so called highly active antiretroviral treatment (HAART).

There are several different methods for determining the sensitivity of HIV to antiretroviral drugs, but no simple standardised method for routine use. All available methods are relatively complex and furthermore the interpretation of the assays is complicated. Thus, the exact consequence of development of resistance is not fully known. It is clear that resistance often leads to loss of treatment effect, but the loss is not always complete.

Although the monitoring of drug resistance is important, especially with more widespread use of ARVs, techniques are currently complex and expensive and their use will be confined to reference centres.

Available methods

Broadly, there are two techniques for determining antiviral sensitivity: biological and molecular techniques. Each of these has advantages and drawbacks. An advantage of the biological assay is that the drug sensitivity of a virus isolate is measured directly, whereas for the molecular assays it is inferred from the presence or absence of mutations known to confer drug resistance. This may be far from straightforward in patients who display complex mutational patterns after treatment with several different antiretroviral (ARV) drugs. However, the biological assays require access to a virus isolate. This in itself is a problem because the isolation process is known to select for certain variants from the population present *in vivo* (28). Furthermore, the isolate used is usually obtained from peripheral blood mononuclear cells (PBMC) and may therefore not be fully representative of the actively replicating virus population which is better represented in plasma. These problems can be circumvented with the molecular assays because they allow direct analysis of plasma virus.

Biological methods for determination of drug susceptibility

The classical way to determine antiviral sensitivity is to isolate virus and test its sensitivity by culture in the presence of different concentrations of the antiretroviral drugs in question. It is customary to express the results as the concentration of drug required to inhibit virus replication by 50% or 90% (i.e. 50% and 90% inhibitory concentration, IC_{50} and IC_{90}). There exist "standardised" protocols for the biological antiviral sensitivity assay such as the ACTG protocol, but these standardised protocols require a lot of manual laboratory work and should not be regarded as kits. Thus, the assay is labour intensive and usually takes a minimum of one month to complete an analysis, even if the actual hands-on time is much less. The method also requires that virus be isolated, which is not always possible. The method requires access to a laboratory facility fully equipped for work with infectious HIV, i.e. biosafety level 3 (BSL3) facility which limits the possibilities for large scale use.

Molecular methods for determination of drug susceptibility

There are a number of published molecular methods for determination of drug susceptibility which can be broadly divided into point mutation assays and sequencing strategies.

Point mutation assays: Commonly used methods to detect point mutations known to be associated with drug resistance include primer specific PCR and a type of mini-sequencing. A commercial point mutation assay based on the line-probe technique (LiPA HIV-1 RT, Innogenetics Murex) has recently been introduced. The major advantage of the point mutation assays is that they can analyse the replicating virus population (i.e. plasma virus) and that they are comparably easy to perform. The necessary equipment is usually limited to a thermocycler for PCR (cost approximately US$10,000). A draw-back is that the assays can only be used to detect predefined mutations.

DNA sequencing: There exist a number of sequencing strategies which can be used to detect the mutations which confer drug resistance. Automated systems such as those supplied by Applied Biosystems or Pharmacia-UpJohn are often used. The "gene chip" technology can also be used. The advantage of the sequencing strategies over the point mutation assays is that they can be used to identify new mutations, in addition to predefined mutations. The sequencing methods are labour intensive and require access to expensive equipment.

Recombinant virus assay

The recombinant virus assay is a third type of assay which combines the biological and molecular assay. In this assay, the gene fragments of interest are amplified from plasma by PCR and co-transfected into permissive cells with a HIV plasmid from which the corresponding parts of the gene of interest have been deleted. Infectious virus, which is reconstituted by homologous recombination, is harvested and tested in a biological assay. The assay is attractive because reverse transcriptase and protease sequences obtained from plasma can be biologically tested on a neutral viral backbone sequence. However, the assay requires a highly developed BSL3 facility in which recombinant viruses can be generated and tested.

Options for different settings

As outlined above there exist several different methods for determination of the drug susceptibility of HIV. At present these assays cannot be recommended for large scale routine use because the interpretation of assays is complicated and because the clinical consequences

of resistance are not fully understood. However, drug susceptibility assays are very important tools in clinics and laboratories actively involved in research on antiretroviral treatment. Even in these settings the choice of antiretroviral regimen to individual patients usually becomes a pragmatic decision influenced by plasma HIV-1 RNA measurements, prior treatment as well as treatment side effects and compliance. Accordingly, drugs susceptibility assays, in contrast to HIV-1 RNA assays, are not advocated in the updated recommendations for antiretroviral therapy of the International AIDS Society-USA Panel (27).

SUMMARY

The laboratory requirements for support of ARV treatment can be set at different levels depending on local circumstances: the epidemiological situation, resources available, existing facilities and the number of staff and their level of training. Providing laboratory services for the safe and effective use of ARV treatment requires a degree of centralisation. While many methods are relatively inexpensive and straightforward, others are highly specialised and require large investments in equipment and well trained staff. A country with a relatively small population may choose to have one centre specialised in the back-up for ARV treatment. In larger countries regional centres may be needed, perhaps complemented by a national reference centre. If these services do not already exist it is recommended that a reliable system be set up in one centre before decentralisation. Small and/or resource poor countries may consider international collaboration in order to meet the necessary requirements. Although the crucial HIV quantification techniques are highly specialised and costly, it is important to bear in mind that much of the back-up and follow-up of ARV treatment can be carried out with simple and well-known method requiring a moderate level of instrumentation.

Facilities have to be available for correct diagnosis of HIV infection, monitoring of CD4 levels in patients, side effects of ARV treatment, identification and diagnosis of opportunistic infections, viral load monitoring and observation of resistance of HIV.

In a **setting with very limited resources**, it is recommended that diagnosis of HIV infection and CD4 T-cell counts be done with alternative methods which are less costly in terms of equipment as well as reagents. These techniques are generally more simple to perform and the analyses required are less complicated. A majority of the adverse reactions to ARV treatment can be monitored by careful clinical examination and a set of basic laboratory tests, such as blood counts including differential, bilirubin and liver enzymes, amylase, urate and glucose (simple dip tests of urine are usually sufficient). Similarly, for appropriate monitoring of opportunistic infections, a well trained and experienced clinician can do this with the assistance of chest X-ray and light microscopy. The latter will include (the relatively inexpensive) reagents for staining of specimens for microbiological diagnosis, e.g. pneumocystis carinii, tuberculosis and intestinal parasites. Monitoring of plasma viral load is an important part of ARV treatment. However in some developing countries CD4 counts will be used for monitoring disease progression and response to ARVs. Viral load provides information on treatment adherence and the development of resistance. The currently available method are expensive and complex but in relation to the cost of the treatment, not preposterous. Less costly and simpler alternatives may be available in the future. The use of CD4 counts, for example, with an alternative method may give useful information but cannot completely replace viral load measurements. It should not be a priority to purchase equipment for detailed analysis of resistance patterns in situations of limited resources.

In a **setting with a higher level of resources**, it will be possible to establish more detailed diagnostic procedures. The addition of endoscopy equipment for example, for gastrointestinal infections, bronchoscopy for pneumocystis carinii, bacteriological cultures including tuberculosis, computed tomography (CT) for cerebral toxoplasmosis, polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) for progressive multifocal leucoencephalopathy (PML) and immunofluorescence for herpes simplex virus infections, will increase the specificity in the diagnosis of opportunistic infections and, thus, lead to more efficient and cost effective treatment of these complications of HIV infection. Determinations of T lymphocyte subsets will benefit from the addition of flow cytometry which is more powerful and flexible than the alternative methods for CD4/CD8 analyses. Alternative methods may be used by smaller units, e.g. at regional centres, while a national reference centre may have flow cytometry equipment. This implies that the different methods have been evaluated and standardised against each other. Monitoring of viral load should be part of the routine services. Which method for viral load measurement to choose is more a matter of available local equipment, experience and preference than differences in performance. It should, however, be noted that the first generation of the Organon and Roche assays may give false low results on subtype A and E samples. The establishment of some type of detailed analysis of ARV resistance may be considered, if not sought through international collaboration.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS)/WHO. Revised recommendations for the selection and use of HIV antibody tests. Weekly Epidem Records 1997;72:81-88.

2. Andersson S, da Silva Z, Norrgren H, Dias F, Biberfeld G. Field evaluation of alternative testing strategies for diagnosis and differentiation of HIV-1 and HIV-2 infections in an HIV-1 and HIV-2-prevalent area. AIDS 1997;11:1815-22.

3. Lyamuya E, Bredberg-Råden U, Massawe A, et al. Performance of a modified HIV-1 p24 antigen assay for early diagnosis of HIV-1 infection in infants and prediction of mother-to-infant transmission of HIV-1 in Dar es Salaam, Tanzania. J Acquir Immune Defic Syndr and Human Retrovir 1996;12:421-426.

4. Sninsky J, Kwok S. The application of quantitative polymerase chain reaction to therapeutic monitoring. AIDS 1993;7 (suppl 2):S29-34.

5. De Vita Jr V, Hellman S, Rosenberg S (editors). AIDS: etiology, diagnosis, treatment and prevention, 4th ed. Lippincott-Raven Publishers, Philadelphia, USA, 1997.

6. van Praag E, Fernyak S, Martin Katz A (editors). The implications of antiretroviral treatments. Informal consultation, April 1997. World Health Organization in collaboration with UNAIDS, Geneva. WHO/ASD/97.2.

7. Centers for Disease Control and Prevention. 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV). MMWR 1997;46(No. RR-2):1-30.

8. Nicholson JA, Velleca WM, Jubert S, Green T, Bryan L. Evaluation of alternative CD4 technologies for the enumeration of CD4 lymphocytes. J Immunol Methods 1994;177: 43-54.

9. Lyamuya EF, Kagoma C, Mbena E, Urassa W, Pallangyo K, Mhalu FS, Biberfeld G. Evaluation of the FACScount, TRAx^{TM} CD4 and the Dynabeads methods for CD4+ T lymphocyte determninations. J Immunol Methods 1996;195:103-112.

10. Wei X, Ghosh SK, Taylor ME, Johnson VA, Emini EA, Deutsch P, Lifson JD, Bonhoeffer S, Nowak MA, Hahn BH, Saag MS, Shaw GM. Viral dynamics in human immunodeficiency virus type 1 infection. Nature 1995;373:117-22.

11. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995;373:123-6.

12. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 1996;271:15826.

13. Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JSG, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG, Volberding PA. Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society - USA panel. JAMA 1997;277:1962-9.

14. Boni J, Opravil M, Tomasik Z, Rothen M, Bisset L Grob PJ, Luthy R, Schupbach J. Simple monitoring of antiretroviral therapy with a signal-amplification-boosted HIV-1 p24 antigen assay with heat-denatured plasma. AIDS 1997;11:F47-52.

15. Alaeus A, Lidman K, Sönnerborg A, Albert J. Subtype-specific problems with quantification of plasma HIV-1 RNA. AIDS 1997;11:859-65.

16. Richman DD, Havlir D, Corbeil J, Looney D, Ignacio C, Spector SA, Sullivan J, Cheeseman S, Barringer K, Pauletti D. Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. J Virol 1994;68:1660-6.

17. Schuurman R, Nijhuis M, van Leeuwen R, Schipper P, de Jong D, Collis P, Danner SA, Mulder J, Loveday C, Christopherson C. Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). J Infect Dis 1995;171:1411-9.

18. Kaye S, Loveday C, Tedder RS. A microtitre format point mutation assay: application to the detection of drug resistance in human immunodeficiency virus type-1 infected patients treated with zidovudine. J Med Virol 1992;37:241-6.

19. Stuyver L, Wyseur A, Rombout A, Louwagie J, Scarcez T, Verhofstede C, Rimland D, Schinazi RF, Rossau R. Line probe assay for rapid detection of drug-selected mutations in the human immunodeficiency virus type 1 reverse transcriptase gene. Antimicrob Agents Chemother 1997;41:284-91.

20. Boucher CA, Keulen W, van Bommel T, Nijhuis M, de Jong D, de Jong MD, Schipper P, Back NK. Human immunodeficiency virus type 1 drug susceptibility determination by using recombinant viruses generated from patient sera tested in a cell-killing assay. Antimicrob Agents Chemother 1996;40:2404-9.

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

Office of AIDS and Sexually Transmitted Diseases (ASD)
World Health Organization
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4613
Fax: 41 22 791 4834

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Guidance Modules on Antiretroviral Treatments

Module 6
The Use of Antiretroviral Drugs to Reduce Mother to Child Transmission of HIV

Joint United Nations Programme on HIV/AIDS (UNAIDS)

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UNAIDS/98.7

Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Glenda Gray and Dr James McIntyre, Baragwanath Hospital, Johannesburg, South Africa, for preparing the text of this module;

Dr Isabelle De Vincenzi, Policy, Strategy and Research, UNAIDS, Dr Elizabeth Hoff, Division of Reproductive Health, WHO, Dr Kevin De Cock, Centers for Disease Control and Prevention, Atlanta, USA, and Dr Felicity Savage-King, Division of Child Health and Development, WHO, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for coordinating the project.

Module 6
The Use of Antiretroviral Drugs to Reduce Mother-to-Child Transmission of HIV

Introduction

Mother-to-child transmission (MTCT) is responsible for 5-10% of the total of new HIV infections each year in many developing countries, with more than 500,000 children being infected each year. The introduction of antiretroviral (ARV) drugs for the prevention of MTCT has dramatically reduced rates of transmission among non-breastfeeding mothers in many developed countries, and continued improvements are being seen as more women enter pregnancy while on combination ARV therapy in developed countries. A recent study has shown that short course zidovudine (ZDV) is also effective and major reductions in the cost of ZDV for use in perinatal transmission interventions have been negotiated. These developments will make ARV therapy for MTCT more accessible than before.

The use of antiretroviral drugs for the prevention of perinatally acquired HIV infection should always be considered in the context of optimal health care for the mother. Emphasis on the provision of high quality antenatal and voluntary counselling and testing services must be seen as prerequisites for the introduction of any MTCT ARV initiative.

The use of zidovudine (ZDV) in either "long" or "short"[1] course regimens has been shown to reduce the risk of mother-to-child transmission of HIV in non-breastfeeding mothers. This represents an important preventive strategy. The use of ARVs in pregnancy for the purpose of preventing transmission should be viewed primarily as part of HIV prevention activities. Although routine treatment with ARVs may not be accessible in all settings for pregnant women, if they are available, the prevention of MTCT should be considered as part of a holistic care plan for the pregnant woman and the child, which extends beyond pregnancy.

1. Transmission of HIV from mother-to-child

At the beginning of 1998, more than thirty two million people were estimated to be living with HIV/AIDS, almost half of whom were women in their reproductive years. Mother-to-child transmission of HIV remains the main mode of acquisition of infection for children. Over one and a half million HIV infected women become pregnant each year, the majority in Africa and Asia, with more than half a million children infected. Between 5 and 10 million children are expected to be infected with HIV by the end of the 1990s. If they survive the first few years of childhood, they are likely to suffer the same fate as the 8.2 million children who have lost their mothers or both parents to AIDS in the epidemic to date. Estimates of MTCT vary from 14-42%[2] in different regions, before the use of antiretroviral therapy. With access to zidovudine during pregnancy, MTCT in the developed world has been reduced to

1 "Long course" as defined by ACTG076 and similar regimens (including pre-natal, intra- partum and post natal components). "Short course" refers to four weeks ZDV given to the mother at 36-40 weeks antenatally.
2 Mother-to-child transmission rates: Zambia 39% (Hira, 1989); South Africa 35-39% , (Lyons 1996); Europe 13%; USA, New York State, 25%, (Dabis et al 1995).

below 9% in mothers who do not breastfeed their babies, with further reductions to below 5% in many areas. In two small studies in developed world settings no transmission has been seen in children born to women receiving ARV monotherapy with elective caesarean section or combination ARV, and not breast-feeding.

Factors affecting transmission

Transmission of HIV[3] can occur prenatally, at the time of labour and delivery or postnatally through breastfeeding. The contribution of each of these routes to overall transmission has not been quantified exactly but it appears that a substantial proportion of infection occurs at the time of delivery. A number of factors are associated with higher risks of transmission. These can be divided into viral, maternal, obstetrical, fetal and infant factors

Viral factors

Transmission is increased by high maternal viraemia, such as in advanced disease and at the time of seroconversion. With the development of new techniques for the measurement of the virus, such as quantitative PCR DNA and RNA, an association has been shown between the maternal viral load and the risk of transmission from mother to child. More than half of the women with viral loads of >50 000 RNA copies per ml at the time of delivery have been shown to transmit the virus, although there does not seem to be a lower limit below which transmission does not take place. The local viral load in cervico-vaginal secretions and in breastmilk may also be an important determinant of transmission risk intrapartum and through breastfeeding. Other characteristics of the virus, such as the genotype and phenotype may be associated with higher transmission risks.

Maternal factors

Maternal risk factors

- Advanced immunosuppression
- Advanced clinical disease
- High viral load
- Recent infection
- Vitamin A deficiency
- Placental barrier integrity: chorioamnionitis

The risk of MTCT of HIV is higher in women with clinical, immunological or virological markers of advanced HIV infection. A low CD4 count or low CD4 percentage correlates with an increased risk of MTCT. Immunological factors such as the presence of neutralising antibodies may play a role in minimising transmission. The involvement of specific T-cell immunity in the pathogenesis of MTCT has yet to be described.

Maternal nutritional factors, such as serum Vitamin A levels have been correlated with the risk of transmission in a Malawi study. The mean vitamin A level in mothers who transmitted virus to their children was significantly lower than in those who did not transmit. The

[3] Throughout this document HIV refers to HIV-1 since cases of MTCT of HIV-2 are extremely rare

mechanism is uncertain, but it has been suggested that vitamin A may maintain the integrity of the vaginal mucosa or placenta and may have immune stimulatory properties. Alternatively, low vitamin A levels may be a marker for other deficiencies or behavioural factors, which influence transmission. Several behavioural factors have also been associated with an increased risk of transmission from mother-to-child. These include cigarette smoking, illicit drug use and high rates of unprotected sexual intercourse with a seropositive partner during pregnancy.

The cellular composition of the placenta changes with gestation, and the risk of placental infection may vary over pregnancy. Placental disruption, for example chorioamnionitis, and cigarette smoking have been associated with increased transmission rates.

Obstetric factors

Delivery factors
- Mode of delivery: vaginal vs caesarean section
- Prematurity
- Prolonged rupture of membranes
- Use of instruments

Obstetric factors are important determinants of transmission, as most transmission takes place around the time of labour and delivery. Several factors have been implicated, although results are not consistent across studies with regard to their relative importance. These include preterm delivery, intrapartum haemorrhage, obstetric procedures, the use of foetal scalp electrodes, episiotomy and vaginal tears. The duration of labour does not appear to be as important as the duration of rupture of membranes, and the transmission risk is doubled with ruptured membranes for longer than four hours. Delivery by caesarean section has been shown to be protective in some prospective follow up studies, but not in all. A randomised controlled trial is in progress in Europe to attempt to answer this question.

Foetal factors:
Preterm infants have higher reported rates of transmission of HIV. The increased risk of infection in premature infants is likely to be due to increased susceptibility to intrauterine acquisition of infection as a result of immaturity of the immune system and low levels of maternally derived HIV antibodies. First born twins have higher rates of infection than second born twins. However this difference is particularly striking in first born infants delivered vaginally (35% infected), when compared with second born twins born by caesarean section (8% infected), highlighting the importance of intra-partum factors in transmission. Other foetal factors may include co-infection with other pathogens, foetal nutrition and foetal immune status.

Breast feeding and infant factors:
Breastfeeding is responsible for a high proportion of mother-to-child transmission in developing countries, where 1 in 7 children born to HIV-positive mothers will be infected through breastmilk. This is less common in the developed world, where most HIV-positive women will not breastfeed. A meta-analysis of studies of transmission through breastfeeding

showed the additional risk of transmission through breastfeeding to be between 7 and 22%, equivalent to a doubling of transmission rates. **Late postnatal transmission**, after the age of three months, has been described and may contribute 4-20% to the overall rate of vertical transmission in breastfed infants according to several studies from Africa.

The risks of postnatal transmission may also be related to other factors in the new-born. HIV may enter through the gastro-intestinal tract following ingestion of virus in utero or at birth. There is decreased acidity, decreased mucus, lower IgA activity and thinned mucosa in the newborn gastro-intestinal tract, which may facilitate transmission. The newborn immune system may also be deficient in macrophage and T cell immune response, increasing the susceptibility to infection. At least part of the effect of antiretroviral drugs in pregnancy appears to be due to a post exposure prophylaxis effect after birth.

In summary, MTCT appears to be governed by an interaction between viral, immunological and other factors such as the mode of delivery, length of rupture of membranes and infant feeding practice. Interventions to reduce MTCT of HIV should target these factors.

2. Strategies to reduce mother-to-child transmission

The only interventions proven to reduce mother-to-child transmission significantly are the use of ARVs and the avoidance of breastfeeding.

ZDV therapy:

The first indication that ARV treatment can help to prevent MTCT of HIV came with the results of the ACTG076 study in 1994. In 1998, results from a short course ZDV study in Thailand showed that a lesser but significant reduction could be obtained with shorter courses of therapy.

Long course, ACTG076

The reduction of MTCT of HIV with zidovudine (ZDV) in the ACTG076 study constitutes a major breakthrough, opening new areas for research and interventions in MTCT. Antiretroviral therapy may decrease viral load and/or inhibit viral replication in the infant. Results from the ACTG076 study, which looked at the effect of zidovudine in pregnancy, during delivery and for six weeks to the infant, support these hypotheses. In this randomised placebo-controlled trial in a non-breastfeeding population, treatment with ZDV (100mg 5 times daily) or placebo was started between 14-34 weeks of pregnancy (median 26 weeks). Women also received intravenous ZDV or placebo during labour and the infants received oral ZDV (2mg/kg qid) or placebo for six weeks. All women had CD4 counts >200 per mm^3, were symptom free and were ZDV naive.

The results of this study show that perinatal transmission can be significantly reduced by the use of antiretrovirals. The first interim analysis on 356 mother-infant pairs demonstrated a reduction in the risk of MTCT transmission from 25.5% in the placebo group to 8.3% in the ZDV group. ZDV achieved a 67.5% reduction in transmission risk. The drug was well tolerated in both the pregnant women and the neonates. The results from the ACTG076 trial and the ZDV in Pregnancy Register show as yet no evidence of teratogenicity or short term adverse effects in the foetus or new-born, but long term follow up is still required.

ZDV in this regimen (or with minor adaptations in the oral dosing regimen) has become the standard of care for prevention of perinatal transmission in HIV infected women in the USA and other developed countries. On the basis of the ACTG076 and the recent availability of new classes of antiretrovirals, further reductions in perinatal transmission may be possible in the developed world with combination therapy.

These results are not applicable to most women in the developing world where most MTCT transmission occurs. This is because of the high cost of the intervention, the logistics of carrying out a regimen requiring intravenous infusions during delivery and therapy to the new-born for six weeks and the need to start the intervention early on in pregnancy, in situations where most women book late. In addition, the ACTG076 trial was conducted in a non-breastfeeding population so the efficacy of the regimen in a breastfeeding population needs to be determined.

The effect of ZDV in this regimen may have been sub-optimal among those pregnant women who received more than 14 weeks of therapy. The initial reduction in HIV viral load induced by ZDV in ZDV-naive patients disappears after an average of 14 weeks of treatment to baseline levels. Therefore, with a shorter regimen (<14 weeks), the reduction in perinatal transmission may be greater.

Short course (CDC THAILAND STUDY)

The ACTG076 regimen has not been implementable in developing countries due to cost and logistical issues. In March 1998, the Bangkok Perinatal ZDV Study announced preliminary results. This study was a randomized placebo controlled trial to evaluate the safety and efficacy of a short course of oral zidovudine (ZDV) administered during late pregnancy and labour to reduce the risk for perinatal HIV transmission. The regimen was of 300 mg ZDV orally twice daily from 36 weeks gestation until the onset of labour and 300 mg every three hours from the onset of labour until delivery. All women were advised *not* to breastfeed and were provided with infant formula, and it is important to bear in mind that these results are directly applicable only to formula fed infants.

397 women were enrolled in the study (198 in ZDV arm, 199 in placebo arm); 4 women were lost to follow up before delivery and 393 women delivered. At enrollment, the median age was 24 years and the median CD4 count was 424 cells/uL. Baseline characteristics were balanced between the two arms. The median duration of antenatal treatment was 24 days and the median number of labour doses was three. Ninety-nine percent of women took at least 90% of pills in the antepartum period, and 99% took at least one dose during labour. 96% of antenatal and post natal study visits were kept by the women. There were 19 routine contacts between health worker and the mother during the antenatal and post natal period.

Fifty-two of the 391 children were infected: 17 in the ZDV arm and 35 in the placebo arm. The Kaplan-Meier estimates for transmission risk in the ZDV and placebo arms were 9.2% (95% confidence interval, 5.0%-13.5%) and 18.6% (95% confidence interval, 13.0%-24.0%), respectively, representing a 51% reduction in transmission risk (95% confidence interval,

15% - 71%).

The Thailand results demonstrate that a short course of twice-daily oral ZDV used from 36 weeks gestation until delivery was safe and reduced the risk for mother-infant HIV transmission by approximately one half. Following the release of the results, Glaxo-Wellcome has announced a major reduction in the price of ZDV for use in prevention of mother-to-child transmission in developing countries, increasing the likelihood of this intervention being implemented.

It must be noted that in both these studies the majority of women were not severely immunosuppressed, adherence to ARVs and clinic attendance was very good and no women were breastfeeding.

2.2 Avoidance of breastfeeding

Few HIV-positive women in industrialised countries choose to breastfeed, but this remains the norm for most infected women in developing countries. This is possibly the major reason for the higher rates of transmission seen in these settings. The additional risk of infection in breastfed infants is estimated to be between 7% and 22%. This must be considered in the introduction of any ARV strategy. The issue of infant feeding is complex, with the need to preserve the benefits of breastfeeding for uninfected women and children, while finding suitable and affordable (in adequate quantities - 20kg for 6 months) breast milk substitutes[4]. Mothers must be given guidance on how to prepare breast milk substitutes as safely as possible and enough clean water, fuel and time to do so.

2.3 Combination ARVs and other interventions

Many of the current interventions being studied are based on the premise that a substantial proportion of HIV transmission occurs in late pregnancy, during labour and delivery. A number of studies are in progress with results expected through 1998 and 1999. These are summarised in Table 1. Results are expected in mid-1998 from the UNAIDS PETRA study (ZDV and 3TC), from the Malawi Vitamin A study and by late 1998 from the randomised study on breastfeeding and the vaginal cleansing with 0.25% chlorhexidine study in Kenya. These results will help in the design of the most appropriate interventions for developing countries. The presence of sexually transmitted infections (STIs) increases viral shedding. Therefore, pregnant women who have concurrent STIs will have higher levels of HIV in vaginal secretions and this may increase MTCT.

4 “Breastmilk substitutes” refer to all alternatives to breast feeding and include commercial formula feeding , home prepared formulas, and modified animal milk feeds
“Artificial feeding” means feeding an infant on breastmilk substitutes.

3. Implementation

There are certain requirements within services that need to be fulfilled to ensure the successful introduction of an antiretroviral strategy for pregnant women.

Minimum requirements for ARV therapy in pregnancy

1. Access to and utilization of appropriate antenatal, intrapartum and post-partum care with adequately trained health workers.
2. Adequate voluntary pre- and post- test counselling services (VCT).
3. Affordable and reliable HIV testing.
4. Acceptance and uptake of VCT by HIV infected women
5. Providing an enabling environment; preventing discrimination and abuse of women who test positive.
6. Continuing medical and social support for HIV infected women.
7. Laboratory services to monitor blood parameters (for the short course regimens haemoglobin estimation at enrollment is sufficient).
8. Delivery units with access to safe standard precautions: disinfectants, gloves and needles.
9. Affordable ARV drugs.
10. A sustainable pharmaceutical distribution and storage system for ARV drugs, to include quality control.
11. The availability of an adequate supply of affordable breastmilk substitutes, counselling about infant feeding options including guidance on how to prepare feeds as safely as possible, access to safe water and fuel for those who choose not to breast feed their infants, for the maximum benefit of an ARV intervention.

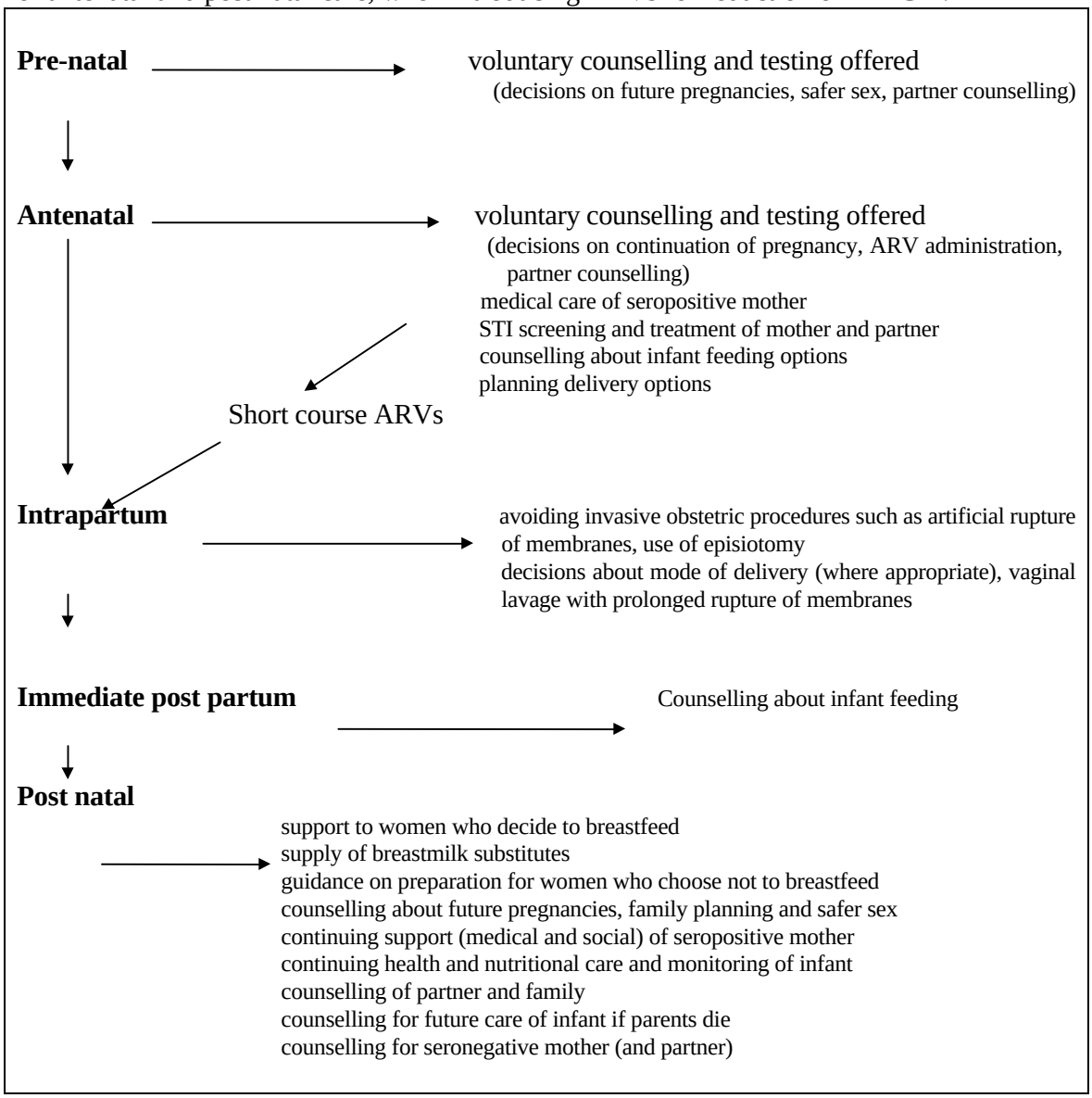
Setting up ARV services in maternal health services

MTCT interventions must be part of a comprehensive approach to HIV prevention and care and to antenatal care. A number of guiding principles should underlie these interventions:

- Primary prevention of HIV infection in women
- Non-stigmatisation of women
- Support services for HIV positive women and children
- The health and well-being of mothers and other children should not be altered by MTCT interventions
- Resources should not be diverted from antenatal care and related programmes

Any ARV intervention will require the identification of HIV positive women at an early enough stage of pregnancy for them to access the intervention. Voluntary counselling and testing (VCT) is thus the cornerstone of an HIV care service for pregnant women, and should be established concurrently if interventions to reduce MTCT are proposed.

The following table highlights the essential activities that need to be addressed at each phase of antenatal and post natal care, when introducing ARVs for reduction of MTCT :



The following steps need to be considered by MCH programme managers before setting up ARV MTCT services:

1. STRENGTHENING ANC AND WOMEN'S HEALTH SERVICES

Currently many women in developing countries are either not receiving antenatal care or are receiving inadequate care. Furthermore, less than 50% of women deliver with the aid of a skilled attendant. It is therefore important to improve access to and quality of ANC services when considering the introduction of ARV interventions.

2. VOLUNTARY HIV COUNSELLING AND TESTING IN PREGNANCY

With increasing knowledge about MTCT of HIV, there has been more consideration of the potential benefits of HIV testing in pregnancy for the individual woman. This has re-emphasised the need for the provision of appropriate facilities for counselling and testing. Voluntary testing of pregnant women is recommended and offered in many countries, but despite this, identification of infected women may be very incomplete if women do not access antenatal care, or if counselling and testing services are inadequate.

Wherever possible, voluntary counselling and testing (VCT) should be available to any pregnant women who request it, and offered to all in areas of moderate or high prevalence. Any testing of pregnant women must be confidential and undertaken with informed consent and with access to ongoing counselling. Issues regarding disclosure of the result need to be considered as ongoing counselling continues in the antenatal clinic. The cost of possible interventions should include the cost of HIV testing as well as the cost of training and supporting counsellors and the cost of employing additional staff.

There are several potential benefits of voluntary HIV counselling and testing (VCT) of women or, even better, couples prior to or during pregnancy: This is the case even in the absence of expensive interventions such as long course antiretroviral therapy.

Advantages of VCT in the antenatal setting

1. Knowledge of the HIV status of a couple or a woman can facilitate early counselling and treatment for the woman, and appropriate treatment and follow up of her child.
2. Knowledge of her HIV status enables the woman to take decisions on continuation of the pregnancy and on future pregnancies.
3. Testing provides an opportunity to implement strategies to reduce transmission to the child.
4. Knowledge of HIV status enables the woman to take precautions to help prevent transmission to sexual partners.
5. If the test result is negative, women can be guided in appropriate HIV prevention measures and risk reduction behaviour.

Balanced against these advantages are the possible disadvantages of HIV testing in pregnancy. An increased risk of violence against women; the possibility that the woman may be stigmatised within her community and by health workers; higher levels of anxiety and psychological sequelae; and concerns about the additional work load for maternity services have all been reported. In the absence of interventions to reduce MTCT many women in high prevalence areas have been reluctant to know their HIV status, but when something can be offered uptake is much greater.

VCT can be provided as part of an antenatal service, or as already exists in some developing countries, as a free standing site. There are advantages in both type of services. VCT services in existing antenatal services may be more convenient for women and uptake levels for this

service may be higher. However VCT in free standing sites are often linked to well established support services for people living with HIV/AIDS (PLHA) and care for seropositive women following delivery may be easier.

Future research should be directed towards making HIV counselling and testing more affordable and accessible to all pregnant women, possibly using salivary HIV testing or other rapid tests that are sensitive, specific and inexpensive. Same day, on-site testing and diagnosis has been shown to be acceptable and accurate, and this may be a suitable approach.

3. ANTENATAL CARE

Antenatal care provides an opportunity to screen for illness and pregnancy complications and to treat existing illness which may affect the outcome for mother and child. Although antenatal care is almost universal in the developed world, access (defined as at least one antenatal visit) in the developing world varies from just under 90% in Southern Africa to 68% and 55% in Eastern and Western Africa respectively. In many of these areas, less than 40% of deliveries are assisted by a trained attendant and only 30% of deliveries take place in health institutions.

The identification of HIV-infected women during pregnancy allows for many beneficial interventions, including the possible introduction of strategies to reduce transmission, as well as specifically improving the health care of seropositive women during the antenatal period. The level of antenatal care coverage, the number of visits possible for each woman and the gestational age at which women present for care will determine the type of MTCT prevention intervention which could be introduced.

Women receiving long course ARV will require haematological and liver enzyme monitoring. With short course therapy the risk of development of anaemia is much reduced and a screening haemoglobin may be all that is required. Combination ARVs have been used less frequently in pregnancy and less is known about the possible risks. For this reason. maternal and foetal monitoring should be more intensive in women on long course combination therapy.

4. ARV REGIMENS IN PREGNANCY

In many developed countries the standard of care for AIDS treatment has become at least two nucleoside analogue reverse transcriptase inhibitors, with the addition of a protease inhibitor. Patients receiving this therapy may have undetectable viral loads. While there has been little experience with these combinations in pregnancy to date, the dramatic lowering of viral load on combination treatment may be beneficial in preventing transmission to the foetus. Pregnancy, per se, should not be a contraindication to the use of the most appropriate therapy and most current guidelines recommend the same treatment for pregnant and non-pregnant women.

Possible schedule for introducing ARVs to reduce MTCT into antenatal care

	First visit - end 4th month; 16 weeks	Second visit – 6th/7th month; 24-28 weeks	Third visit – 8th month; 34-36 weeks	Fourth visit – 9th month antenatal care	Delivery
Respond to symptoms	✓	✓	✓	✓	✓
Screen for risk factors	Take history; observe scar etc.		Assess; obvious multiple pregnancy	Assess; lie, multiple pregnancy	
Screen and treat as needed **HIV testing**	Anaemia, BP, RPR HIV pre-test counselling /testing	Anaemia, BP ↔HIV testing	Anaemia, BP	Anaemia, Hb, BP	
Prophylaxis	Mebendazole Iron Check/Give Tetanus Toxoid Immunisation	Anti-malaria prophylaxis Iron +folate Check/Give Tetanus Toxoid Immunisation (TT2)	Anti-malaria prophylaxis Iron +folate Oral Zidovidine 300mg bd 36 weeks until delivery	Anti-malaria prophylaxis Iron +folate Oral Zidovidine 300mg bd 36 weeks until delivery	Intensive treatment with oral Zidovidine 300mg every 3 hours from onset of labour until delivery
Counsel individually	Where to give birth Results RPR Benefits of VCT	 Post test counselling & Test results Refer to support groups	 Infant feeding counselling If positive - ARV therapy (consent)	Birth Plan Decision on infant feeding Adherence issues	Breast feeding techniques Support mothers' decision on breastmilk substitute
Advise	Obtain clear delivery kit When to seek care	How to prepare for birth Plan for emergency	If home delivery planned; safe steps	Check if obtained clean delivery kit	Refer positive women for care & social support
Plan for follow-up	Next visit – Routine Bring partner	Next visit – routine	Follow-up after birth; (child immunisation) EPI		Family planning, possible partner/family counselling

It is important to note that this regimen has only been shown to be successful in reducing MTCT in non-breastfeeding populations so at present mothers taking ARVs must be counselled on alternatives to breastfeeding. In settings where mothers are unable to afford formula milk, free or subsidised commercial infant formula should be provided. A system for distribution and supply of both ARVs and infant formula will have to be organised. Both these will have high resale values may be misappropriated for other uses so secure storage and distribution will have to be ensured. (See Module 8 for more information on the regulation, distribution and control of ARVs). If infant formula is provided, strict controls must be in place and it must be distributed according to the provisions of the International Code of Marketing of Breastmilk Substitutes. (See *HIV and Infant Feeding*, WHO/FRH/NUT 98.1)

5. INTRAPARTUM CARE

Prolonged rupture of membranes should be avoided, as should any invasive monitoring such as penetrative scalp electrodes or fetal scalp blood sampling and invasive obstetric procedures such as artificial rupture of membranes and episiotomy. In a study from Malawi, vaginal cleansing with 0.25% chlorhexidine during labour has been shown to reduce the neonatal and puerperal sepsis rates, and to reduce HIV transmission where membranes are ruptured for longer than four hours. Where available, elective cesarean section may reduce the risk of MTCT.

6. POSTPARTUM CARE

Postpartum care for HIV positive women should include continued counselling about infant feeding, risks of transmission, family planning provision and support for the mother and the family. Few HIV positive women choose to breastfeed in developed countries. In resource poor settings, alternatives to breastfeeding may not be feasible for financial, logistical and cultural reasons. In societies where breastfeeding is the norm mothers will need particular support if they choose to use breastmilk substitutes. They will need careful guidance about how to prepare feeds accurately and safely, how to cup feed their infants, clean utensils and introduce complementary foods (See *HIV and infant feeding* WHO/FRH/NUT 98.1). Health workers will need to be trained to provide this guidance. Mothers may need to cope with the stigma of artificial feeding in societies where it is not commonly acceptable. Furthermore, women who decide to cup feed may be subject to speculation about their HIV status and the resulting stigma and discrimination. Mothers should be given information on the advantages and disadvantages of breastfeeding with regard to HIV infection, and encouraged to make a fully informed decision about infant feeding, prior to delivery. They should be suitably supported in their decision, which may include providing free or subsidized breastmilk substitutes on prescription.

Problems associated with artificial feeding

- Cost, supply, distribution and control
- Risk of morbidity and mortality
  - lack of clean water, fuel, time, bottles/feeding cups
  - lack of immunological benefits of breast milk
- Cultural acceptability, stigmatisation
- Common knowledge of mother's serostatus
- Undermining breastfeeding in HIV-uninfected (or untested) population

The risk of infant feeding with alternatives to breastmilk should be less than the potential risk of HIV transmission.

Infections may be more common in the postpartum period and women should be told about the signs and symptoms of these in order to seek care early. Where ARVs are available for treatment of adults, mothers should be evaluated to determine the need for appropriate ARV therapy for their own HIV related disease. Where ARVs are not available for general use other treatments for HIV disease and prevention of opportunistic infections (OIs) can be of great benefit to seropositive women.

7. CARE OF INFANTS

Anaemia has been the most common complication seen in the neonate with the long course treatment of six weeks ZDV. Haemoglobin should be measured at baseline and after six weeks and twelve weeks if this regimen is used. The risk of anaemia is much less with the short course therapies. Infants receiving ARVs may experience a transient elevation of hepatic transaminases. There is less experience with the use of combination therapy in the pregnant mother and the risk of toxicity to these infants, and more intensive haematological monitoring is advisable.

Mothers should decide on infant feeding practice before delivery and be supported in their choice. Those who choose to breastfeed should be warned about the possible increased risk of HIV transmission from breastmilk if the infant has oral thrush, or in the presence of cracked nipples or breast abscess and need to be counselled on good breastfeeding techniques in order to avoid these problems. Women who choose artificial feeding for their infants must be given guidance on their accurate and safe preparation in order to avoid morbidity and mortality due to inadequate amounts and contamination.

Children should be referred for long term follow up, health and nutrition care, and for repeat testing for diagnosis of HIV infection, either by early polymerase chain reaction (PCR) or viral culture if available, or by HIV antibody testing at 15 to 18 months, when maternal antibodies will have disappeared.

Although with ARV treatment the number of infants who contract HIV will be greatly

reduced, a proportion will still unfortunately develop HIV disease. They will need continuing medical care and the mother and family will need social and emotional support. Although some infected babies will become sick and die quickly many appear healthy and HIV-related symptoms may not be apparent for many months or years after birth. In industrialised countries the oldest children who were infected perinatally are now 17 years old.

In developing countries where ARVs are not generally available to treat HIV infection in mothers, children who are not HIV-infected are very likely to become orphans. Although this may be a difficult area to explore with mothers, studies have shown that women value guidance from counsellors about making plans for their children's future care and help with making wills so that their children benefit from any material resources.

8. CONTINUING COUNSELLING AND CARE OF SEROPOSITIVE MOTHERS

As stated earlier one of the benefits of VCT for women attending antenatal care is allowing women who test seropositive earlier access to treatment and care. Symptomatic treatment, prevention of OIs and palliative care should be available across a continuum from hospital to home, and appropriate referrals made accordingly. Access to family planning services and condom supplies should also be considered an integral part of this comprehensive care. Seropositive women can be referred by their health care worker to social services and support groups in the community where available.

It is important that seropositive mothers are not "blamed" for their HIV infection. Where possible their partners should also be counselled and offered VCT. Up to 25% of couples in some developing country settings have been found to have discordant HIV results. For discordant couples advice about preventing HIV transmission by using safer sex has been shown to significantly reduce the rate of transmission to the uninfected partner. However, it is important that HIV counselling of partners be voluntary and that women who are ready to disclose their positive status not be subjected to abandonment and abuse.

9 . CONTINUING COUNSELLING AND SUPPORT FOR SERONEGATIVE WOMEN

Even in high prevalence areas the majority of women attending antenatal clinics will test seronegative, but without continuing support, counselling and provision of condoms, many will acquire HIV. If they are pregnant or lactating, they should be encouraged to practice safer sex as the risk of MTCT is especially high with new infection.

Resistance and the use of antiretrovirals in pregnancy

Women who have received extensive prior ZDV therapy may be infected with viral strains that have reduced susceptibility to ZDV. These resistant strains may be transmitted from mother to foetus but the frequency with which such transmission occurs is uncertain, although there are reports that resistant strains are more likely to be transmitted to infants. The effectiveness of ZDV in reducing HIV transmission may be decreased for mothers in whom ZDV resistant strains predominate but this assumption is not yet supported by data. In

the developing world few women will have had prior access to antiretroviral therapy before becoming pregnant, therefore resistance may be less of a problem than that seen in the USA

or Europe.

Concerns about the potential long-term adverse effects among women include the development of ZDV-resistant virus when ZDV therapy is used intermittently to reduce perinatal transmission, especially if used for more than one pregnancy, and the potential effect such resistance could have on disease progression. Even brief exposure to ZDV may decrease the effectiveness of the drug if used again. Similarly prior long term treatment with ZDV has been shown to decrease the potency of d4T plus 3TC more than ten fold. Although the results of some studies have demonstrated an association between emergence of ZDV resistance and total duration of ZDV exposure, none of the study designs have specifically addressed the effect of intermittent therapy on the development of resistance, or of the shorter antenatal regimens in the development of resistance. It is known that when a drug whose use has led to selection of a resistant viral population is withdrawn from the patient, selection forces favour the return of the wild type virus. How quickly the drug resistant mutant virus disappear from the peripheral circulation is predicted by the replication rate of the mutant form versus the wild type. However it appears that "memory" of this prior resistance is retained and the effect of this background resistance is often a very rapid reappearance of the drug-resistant form if the drug is re-instituted

As the clinical implications of resistance to ARV therapy become more obvious, new assays make it possible to measure these events in patients. How these tests should be employed and how considerations of drug resistance may affect the choice of drug remain unclear. Serial CD4 counts and estimates of viral load help elucidate the phenomenon of drug resistance. Resistance testing of any type will have to be interpreted against a background of previous drug therapy, duration of current therapy and the adherence of the patient.

ACCEPTANCE AND ADHERENCE

Acceptance of testing and treatment in the developing world needs to be studied further. In some reports (e.g. in a study from Kigali), the willingness of clinic attendees to know their HIV status was considerable, where two thirds of women tested in 1992/93 returned for post-test counselling. This is in contrast to findings in Cote d'Ivoire, where although antenatal attendees consented to testing, a substantial proportion of women did not return for their results or for post-test counselling. The implementation of an ARV regimen in poorly-resourced, overburdened midwifery/obstetrical units will depend on the number of women consenting to testing and returning for their results, on the simplicity of the regimen (oral dosing, absence of an intrapartum arm and minimal management in labour) and the ease with which they can return for follow-up. Adherence will depend on how easy the regimen is, for example, the use of a single agent vs. multiple agents, oral dosing, daily or twice daily doses vs. multiple doses during the day, if there is a need to take it with/out food and if there are minimal side-effects. Adherence is enhanced if the healthworker and the client understand the regimen and its benefits. Seropositive women receiving ARVs to reduce MTCT may decide to share them with a sick partner or friend, so counselling must include information on the dangers of sub-optimal or intermittent dosing.

CONCURRENT TREATMENT OF WOMEN WITH COMBINED ARV THERAPY

The use of antiretroviral drugs for the prevention of perinatally acquired HIV infection should always be considered in the context of optimal health care for the mother. In

industrialised countries (and under some circumstances in developing countries) some women who become pregnant will already be taking ARVs for treatment of their own HIV infection. Where available and when indicated, appropriate ARV therapy should not be withheld because of pregnancy. Many pregnant women who are taking combinations of ARV drugs have reduced their viral load beyond detection. This may be of benefit to both foetus and mother. The management of combination ARV therapy during pregnancy is complex: only scanty data are available, safety in the first trimester of pregnancy has not been established and there are no controlled efficacy data yet for combination therapy. However data is currently being collected from women using ARVs during pregnancy and adverse effects quantified. The PACTG 219 study is also following children born to mothers who have taken ZDV and other ARVs during pregnancy.

ETHICAL ISSUES

Questions have been raised regarding the ethics of stopping antiretrovirals after delivery. The primary reason for using antiretrovirals in pregnancy is to reduce MTCT and the effects they may have on the mother's health are secondary. ARV use for this indication should be provided for all women regardless of their clinical status, and some of these women would not require ongoing ARV treatment at this stage.

In settings where access to antiretrovirals is not the norm, the cost of continuing these drugs for the duration of the mother's life is likely to be prohibitive. None the less governments, health ministries, pharmaceutical companies and international agencies should endeavour to make these drugs available to people in areas where the majority of HIV infection occurs. Strategies to reduce perinatal transmission will identify large numbers of HIV positive women who should be able to receive ongoing care of the standard available in their communities.

COST-EFFECTIVENESS OF ARV TREATMENT FOR PREVENTION OF MTCT

ARV Treatment	Cost/DALY (US$)	Place, Date of Data, and Source
Prophylaxis for HIV+ pregnant women (076 protocol)	approx. $40-60 (depending on life expectancy)	Model for "a developing country" (Mansergh et al 1996)

An economic assessment of the cost effectiveness of "long" course ARV regimen is shown above. These figures are based on the full price of ZDV and 3TC and will decrease somewhat with price reductions announced by Glaxo Wellcome. No allowance is made for the cost of infant feeding counselling and guidance, or for nutrition support after 6 months of age.

MONITORING AND QUALITY CONTROL OF ARV INTERVENTION

As noted above data on the prevention of MTCT by ARV interventions is either from industrialised countries or from trial settings. It is important that when ARV interventions are adopted in routine health settings that systems are in place for their monitoring. Both operational and efficacy factors must be considered.

Conclusion

Antiretroviral therapy in pregnancy, both in long course and short course regimens, has been shown to significantly reduce the rate of mother-to-child transmission for non-breast feeding mothers. The combined effects of ARV treatment, elective caesarean section, and formula feeding (or other combinations of alternative obstetric and infant feeding practices) are still to be determined. Short course ARV treatment, with ZDV alone has been shown to be effective in a non-breastfeeding population. Additional work on short course monotherapy and combination therapy will provide further information during 1998.

The significant reduction in the price of antiretrovirals for use in the prevention of mother-to-child transmission negotiated by UNAIDS for developing countries will make access to this preventive strategy available to many more women across the world. Drug supply alone is not enough to provide the service, and antenatal care services, voluntary counselling and testing services will be required as a starting point to identify infected mothers. Costs of administering the treatment and of alternative infant feeding options must also be taken into account.

The potential benefits in the reduction of infected infants are of great importance to countries with high HIV seroprevalence, and the early identification of infected women, allowing for appropriate treatment and the adoption of protective measure will provide secondary benefits.

Table 1:
CURRENT RESEARCH ON PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

STRATEGY	RESEARCH PROJECTS
A: ANTIRETROVIRAL THERAPY	Phase III: 1. PETRA: ZDV & 3TC 2. ZDV alone in short course in breastfeeding women 3. Nevirapine (HIVNET 012 & PACTG 316) 4. ZDV short course with early weaning Phase I/II: Drugs under investigation include: ddI, d4T, nevirapine, nelfinavir, ritonavir, indinavir, saquinavir, PMPA, MKC-442
B: ACTIVE IMMUNIZATION	1. Recombinant Gp120 vaccine to pregnant women (PACTG 235). 2. Recombinant Gp120 to new-borns ; phase I/II (PACTG 230) 3. Canary pox vaccine to new-borns (PACTG 327)
C: PASSIVE IMMUNIZATION	1. HIVIG (Uganda) 2. Phase I Katinger antibody
D: MICRONUTRIENTS	1. Vitamin A (Malawi: 10 000IU) 2. Vitamin A South Africa (5000 IU + B Carotene 30mg) 3. 13 Micronutrients (Zimbabwe) 4. Factorial design Vitamin A & B Carotene (Tanzania)
E: VAGINAL CLEANSING	Chlorhexidine (Kenya)
F: INFANT FEEDING	Randomised trial of breast vs formula feeding (Kenya)

Table 2:
FDA classifications of antiretroviral drugs for use in pregnancy

Classification:

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the foetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters)

B: Animal reproduction studies fail to demonstrate a risk to the foetus but well controlled studies of pregnant women have not been conducted

C: Safety in human pregnancy has not been determined, animal studies are either positive for foetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the foetus

D: Positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

X: Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit

DRUG	FDA CATEGORY
Nucleoside Reverse Transcriptase Inhibitors	
Zidovudine (ZDV, AZT)	C
Zalcitabine (ddC)	C
Didanosine (ddI)	B
Stavudine (d4T)	C
Lamivudine (3TC)	C
Non-nucleoside Reverse Transcriptase Inhibitors	
Nevirapine	C
Delavirdine	C
Protease Inhibitors	
Indinavir	C
Ritonavir	B
Saquinavir	B
Nelfinavir	B

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

Office of AIDS and Sexually Transmitted Diseases (ASD)
World Health Organization
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4613
Fax: 41 22 791 4834

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Guidance Modules on Antiretroviral Treatments

Module 7
Treatments Following Exposure to HIV

Joint United Nations Programme on HIV/AIDS (UNAIDS)

World Health Organization (WHO)

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UNAIDS/98.7

Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Elizabeth Bouvet, and Dr Anne Laporte, Hôpital Bichat-Claude Bernard, Paris, France, for preparing the text of this module;

Dr Isabelle De Vincenzi, Policy, Strategy and Research, UNAIDS, Dr Kevin De Cock, Centers for Disease Control and Prevention, Atlanta, USA, and Dr Noel Gill, Public Health Laboratory Services, London, UK, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for coordinating the project.

Module 7
Treatments Following Exposure to HIV

Note on terminology

Accidental exposure to blood (AEB) *is defined as any contact with blood or body fluid as a result of injury with a needle or any other sharp instrument, or via mucous membranes (eye, mouth), or contact via damaged skin (eczema, wound).*

The term ***percutaneous exposure (PE)*** *is used when there has been exposure through non-intact skin.*

Needle stick injury *refers to puncture with a needle or sharp instrument that is contaminated or potentially contaminated with blood.*

Blood splash *refers to skin visibly contaminated with blood.*

Facts and figures

Introduction

Viral transmission due to percutaneous exposure to blood in a hospital occurs in three ways: exposure of health workers to blood of patients; exposure of patients to blood of health workers; exposure of patients to blood of other patients. In practice, the exposure of health workers to blood of patients is the major concern and alone, justifies a specific prevention and surveillance strategy.

The rate of occupational transmission of HIV infection to health workers depends on the prevalence of infection in patients; the frequency of exposures to blood; and the risk of transmission. The **prevalence of HIV infection** varies enormously between different hospital populations (up to 70% of inpatients with tuberculosis in an urban setting in Zambia compared with <0.1% in a geriatric ward in the UK). **Frequency of exposures** is difficult to estimate because of under-reporting of accidents by health personnel and inaccuracies in recall in retrospective studies. It can only be estimated through enquiries undertaken at different points in time or by active surveillance based on sentinel surveys within particular hospitals. Whilst the **risk of transmission** per exposure is low, the risk for a health worker, frequently exposed to the blood of patients in a high prevalence area, may be significant. The risk of transmission is about the same for each percutaneous exposure - around 1-5 per 1000 exposures (0.3%).

Prevention of exposure remains the most effective measure to reduce the risk of HIV transmission to health workers. The priority therefore must be to train health personnel in prevention methods (**universal precautions**) and to provide them with the necessary safe materials and protective equipment. The use of antiretroviral post exposure treatment only makes sense if universal precautions are widely taught and practised so as to reduce the occurrence of exposures to a minimum.

Frequency of percutaneous exposure (PE)

The reporting and description of accidental exposures of all kinds is an essential first step in prevention. The risk of transmission of HIV from PE has been known since the beginning of the AIDS epidemic. The risk for each exposure is relatively low compared to the risk of transmission of other infectious agents such as hepatitis B and C. Given the prevalence of these viruses in the world, the risk of infection with hepatitis B and C is much higher than with HIV and should not be neglected.

Risk of transmission of bloodborne viruses to health care workers following a single exposure	
HIV	
Percutaneous exposure	0.3%
Mucocutaneous exposure	0.03%
Hepatitis B virus (HBV)	
Percutaneous exposure	9-30%
Hepatitis C virus (HCV)	
Percutaneous exposure	1-10%

Most of the current epidemiological data come from developed countries and are based on studies undertaken by the Centers for Disease Control and Prevention (CDC) and EPINet (USA), the Communicable Disease Surveillance Centre (CDSC) in the UK, the Italian Study Group on Occupational Risk of HIV infection and the Groupe d'Etudes sur le Risque d'Exposition au Sang (GERES) in France. Data on the frequency and risk factors for PE to blood in health care systems in developing countries are limited, with the exception of a recent study from Tanzania in nine hospitals in the Mwanza region.

Incidence of AEB and PE reported in the literature*

Study	***Incidence of AEB/PE***
Nurses in France (Abitboul 1993)	27 AEB/100 nurses/year and 21 PE/100/year**
Nurses in Tanzania (Gumodoka 1997)	487 PE/100 nurses/year
Medical students in USA (Jones 1990)	50 PE/100 students/year
Radiologists in USA (Heald 1990)	50 PE/100 radiologists/year
Doctors in USA (Heald 1990)	60 PE/100 doctors/year
Doctors in Tanzania (Gumodoka 1997)	68 PE/100 doctors/year
Anaesthetists in USA (Heald 1990)	130 PE/100 anaesthetists/year
Senior surgeons in USA (Heald 1990)	38 PE/100 surgeons/year
Surgeons in France (Antona 1993)	1000 AEB/100 surgeons/year
Surgeons in USA (McCormick 1991)	600 AEB/100 surgeons/year
Surgeons in Saudi Arabia (Hussein 1988)	420 AEB/100 surgeons/year
Surgeons in Tanzania (Gumodoka 1997)	1474 PE/100 surgeons/year

* References available from WHO

**In 1991, the incidence was 40 AEB and 32 PE/100 nurses/year

The incidence of AEB/PE varies greatly by type of health care worker (HCW)[1], country and year of study. These differences may be due, in part, to different methods of reporting and different definitions of AEB. In high income countries, prevention measures in health care institutions have contributed to a significant decrease in incidence of PE - nearly 40% in France in two years. In Tanzania, the rate of PE among nursing staff was reported to be 20 times higher than in France, but only 50% percent higher among doctors.

Note also the differences between sites in risks of transmission after a single exposure and the risks of exposure to HIV infected blood. In developing countries with high seroprevalences amongst inpatients, the risk of transmission from all PE will be significantly higher.

Risk factors

General patient care

Most studies show that among health workers, AEB occurs most frequently among nurses in hospital settings. Prospective studies undertaken by GERES estimate 30-40 AEB per 100 nurses/year. In the EPINet study undertaken in nine hospitals in the USA, nurses reported 52% of all AEB whilst doctors and interns reported 9% each. Exposures associated with giving of injections account for most AEB in nurses (75% on average). The rate of AEB is much lower for doctors and nursing auxiliaries (around 10 times lower in the first GERES study for these two groups). In the Tanzanian study 434 health workers were questioned on two occasions at 4 week intervals. It was found that 9.2% of nurses but only 1.3% of doctors had had a needle stick injury in the week preceding the interview. The average incidence of needle stick injury in this study was 9.5% per week or 5 per person per year. However, studies done in the USA and in Denmark found a PE rate higher for doctors than for nurses. Again differences in rates may be due in part to different methods of reporting and different definitions of AEB.

Surgery

Outside general patient care, surgeons in operating theatres are the most at risk for AEB. Various studies have attempted to estimate the incidence of AEB in operating theatres. The rate of exposure per operation varies from 5.6% and 30.1% between studies and for different operations. For surgeons, cutaneous exposure or blood splashes are much more frequent than injection injuries. A study from Grady Memorial Hospital of Atlanta (USA) found that 90% of blood contacts were cutaneous and presented a relatively low or negligible risk: 55% on clothes, 37% on non-protected skin, 8% on hands with torn gloves: whereas 10% were of a moderate/higher risk: 7% were through injections or cuts and 3% were in the eye. In the Tanzanian study, the frequency of needle stick injuries reported by surgeons was low (only 3 needle stick injuries for 488 surgical acts: 0.6%) but examination of surgeons' gloves after the operation showed that in 10% of cases these were pierced after the operation.

Students are particularly at risk. Medical students have been shown in several studies (USA, France, Zambia and Israel) to have frequent AEB. According to a study undertaken in two

[1] Health care worker (HCW) - term used to include all workers in health care situations, including nurses, laboratory staff, physicians, surgeons, traditional medical practitioners etc.

faculties of medicine in Paris in 1995, 31% of students in 4-6th year have had an AEB during their clinical training. Although they often have good knowledge about HIV transmission and occupational risks, their inexperience makes them particularly vulnerable. In Zambia medical students report being reluctant to assist with operations or put up drips because of worries about HIV infection. Student nurses are similarly at risk.

In developing countries, there have been few studies of AEB. In Africa, midwives have frequent AEB. Prospective studies in the field are required to investigate the circumstances of accidents in these countries and adapt prevention methods.

High risk procedures

Blood taking
The rate of PE from various procedures varies little from study to study: in general medical care, half of AEB occur during blood taking.

Suturing
Suturing is often reported as a high risk procedure for AEB. In the operating theatre, studies show that most AEB occurs towards the end of the operation, during closure. Suturing is a risky procedure: the suturing needle is responsible for 60% to 80% of percutaneous injuries in surgery. Repair of post-partum tears and episiotomy are high risk events/procedures.

Inadequate disposal of sharps
In general patient care, 30% to 70% of accidents occur when injecting or suturing equipment ("sharps") is thrown away in a container. Other accidents occur during procedures and are therefore dependent on the safety of the instruments themselves. Accidents following procedures are avoidable and indicate poor application of universal precautions. Most sharps injuries occur when needles are recapped or cleaned or when the container for instrument disposal is full, badly made or the opening is too small for the sharps to pass easily. Finally accidents may be caused when used sharps are left on trolleys, beds or other surfaces.

The application of universal precautions should prevent the majority of these accidents.

Risk of HIV transmission following exposure
Prospective studies of health workers exposed to HIV contaminated blood have shown that the rate of transmission after percutaneous exposure is estimated at 0.3% and after cutaneous-mucosal exposure at 0.03%, or 10 times lower. The factors influencing risk of contamination with HIV after accidental exposure to blood are well known.

In a case control study done by the CDC in collaboration with the UK and France, regression analysis revealed that the following factors were independently associated with risk of transmission:

Deep injury	OR 15.0	(95%CL: 6 - 41)
Visible blood on instrument	OR 6.2	(95%CL: 2.2-21)
Procedure involving needle in artery or vein	OR 4.3	(95% CL: 1.7- 12)

Terminal illness in source patient	OR 5.6	(95% CL: 2 -1 6)
Post exposure zidovudine	OR 0.19	(95% CL: 0.06-0.52)

OR: Odds Ratio
CL: Confidence Level

Other risk factors, not identified in this case control study, also probably play a role:

- the time interval between use of needle and the exposure
- the wearing of gloves.

When gloves are worn, it appears that some of the blood contained in the needle is absorbed as it passes through the glove: the reduction in volume of injected blood into the health worker is around 70% or more for a suturing needle but only 35% to 50% for a hollow needle. Wearing gloves may therefore, decrease the risk of transmission after needle stick injury by reducing the viral inoculum injected. Viral load which is related to the clinical status of the source patient, probably accounts for the variability of risk of transmission.

By the end of 1995, 144 cases of HIV infection, assumed to be occupational, and 79 documented seroconversions had been reported in *industrialised* countries. Most seroconversions occurred in nurses (47%). Technicians taking blood in laboratories were the second highest risk group (22%).

Data on post exposure prophylaxis

Effectiveness of antiretrovirals
In 1990, the CDC published recommendations for health workers in case of percutaneous exposure and included the possibility of treatment with zidovudine (ZDV, formerly known as AZT). At that time, the treatment could not be recommended as there were no data in humans on efficacy or safety of ZDV for this indication. However, in many industrialised countries, hospitals dealing with high numbers of cases of HIV infection, had in anticipation of national recommendations, began offering ZDV in 1988.

Today we know that ZDV taken after exposure to HIV can reduce risk of HIV infection post exposure. The CDC study is the only study, so far, to demonstrate effectiveness of ARV treatment as post exposure prophylaxis. The study included 31 cases of seroconversion and 679 controls (exposed people who had not seroconverted); the exposures had occurred between 1988 and 1994. Nine cases (29%) and 246 controls (36%) had taken ZDV. The dose in most cases was 1000 mg ZDV per day for 3 to 4 weeks. Having taken ZDV was a significant factor related to reduction of infection risk (adjusted OR 0.19 - 95% CL:0.06-0.52). The results show that taking into account other factors, the risk of transmission was reduced by 79% (95% CL 43-94%) for those who took ZDV.

The results of this study should be interpreted with some caution. It was not a prospective randomised efficacy study - which would have provided the best answer. However, such a study would not be feasible now given the large number of subjects required and the ethical problems associated with giving a placebo when an effective treatment exists. The study had

very few cases which furthermore, came from different sources. However, even though it may be difficult to determine the exact level of protection from this study, it is nevertheless highly probable that the protection conferred is significant.

Analysis of prophylaxis failures in cases of occupational exposure

Among the nine failures in the case control study (patients infected despite treatment), eight resulted from percutaneous exposures and one mucosal exposure. For the eight percutaneous exposures, ZDV was started between 30 minutes and 12 hours following exposure, for the mucosal exposure, on the 8th day. The daily dose varied between 800 and 1200 mg (median 1000 mg) for 8-54 days (median 21). Two cases of early cessation of treatment were due to development of primary infection. Detailed information about the source patient was available in only four cases: in all four cases, the source patient was at an advanced stage of infection (CD4+ <50/mm3 in 3 cases). In the majority of cases, the source patient was known to have taken ZDV prior to the exposure episode and thus resistance to ZDV may have developed. The sensitivity of the HIV strain to ZDV was only known for two cases, and in these cases, it was shown to be reduced.

Five other cases of failure of PEP with ZDV in non-health workers have been reported, all involving larger quantities of blood than in the percutaneous exposures: a case of blood transfusion from an infected donor, an attempted suicide by inoculation with 2-3 ml of blood from an AIDS patient, a prison guard attacked with a syringe containing infected blood, and two accidental inoculations of contaminated blood during nuclear medicine procedures.

Toxicity and side effects

A data base of records of health personnel from many countries who have received PEP exists and provides estimates of the incidence of side effects of treatment. Most of the currently published data describes monotherapy with ZDV. The Italian National Register had recruited 674 health workers by December 1995. 49% reported at least one side effect and 20% stopped the treatment because of these effects. The most frequently reported symptoms were: nausea (74%), vomiting, abdominal pain, headache and fatigue. The symptoms were dose dependent and reversible with cessation of treatment. They were reported most frequently in the first week of treatment.

Minor anomalies of liver function and haematology were also observed in a minority of cases. In 2% of cases, transaminases increased transiently up to 3 times the normal level and in 3% of cases, anaemia grade 1 (Hb 9.5-11 g/dl) was diagnosed. These disorders appeared after an average, respectively, of 26 days (median 21) and 24 days (median 21) of treatment. Patients did not have to stop treatment and the abnormalities disappeared after the end of treatment. Other minor symptoms, such as skin rash and fever, are common (see modules 4&5). The side effects of PEP are, in the short term, generally moderate and reversible with modification of the dose and/or stopping treatment. However, the long term toxicity of ZDV prophylaxis has not been evaluated.

Prevention

Application of universal precautions

The reduction of AEB in general patient care and laboratories consists essentially of decreasing contact with blood. This is the objective of universal precautions (UPs) which apply to all

services and patients. The recommendations of UPs are guided by a general principle which considers blood *a priori* to be contaminated, a substance with which one should not have direct physical contact.

Universal precautions

Gloves should be worn for
- any contact with body fluids
- any contact with cutaneous or mucosal lesions
- any contact with contaminated, or potentially contaminated material.

All wounds should be covered

Wash hands
- immediately after any contact with potentially infective fluids
- after every health care procedure.

Wear protective clothing (masks, goggles & aprons) when there is a risk of splashing
- tracheo-bronchial aspiration
- endoscopies
- catheritisation
- surgery
- deliveries.

Care when handling potentially infected sharps
- needles should never be bent back or put back in their original holder
- needles should not be removed by hand from syringes or vacutainers
- needles and other sharps should be disposed of immediately in a special, puncture proof,
- sealed container (sharps box).

Disinfection of surfaces

Soiled instruments and surfaces soiled with blood or other bodily fluids should be disinfected immediately with a fresh 1:10 bleach solution or other effective disinfectant.

Disposal of contaminated material

Contaminated material should be placed in distinctively labelled sealed packaging and then incinerated.

Laboratory settings

The above precautions should take place systematically for all samples; samples should be transported in hermetically sealed tubes or flasks, inside sealed packaging; mouth pipetting is forbidden.

Organisation of work: integration of safety measures

Application of UPs, and provision of a strategy to prevent exposures in general patient care, requires various prevention tools and procedures. AEB prevention depends on good organisation and appropriate use of safe materials and equipment. All health care institutions should integrate safety measures into all activities and procedures in all hospital services, inpatient, outpatient and laboratory.

The integration of safety measures into hospital procedures must be designed and agreed upon by a cross section of health care workers. They must identify the causes of accidents reported in the institution and take into account the type of procedure involved, and the availability of

protective equipment. For example, provision of large containers will not be useful unless procedures are reorganised so that there is always a trolley holding the container next to each patient while taking blood. Likewise there is no point in introducing large sharps containers if the opening of the incinerator is too small to take them.

Analysis of AEB in health workers has allowed manufacturers to design protective equipment to limit the risk of contact with blood, in particular to minimise needle stick injuries. Many medical procedures (such as venepuncture, arterial blood sampling, inserting drips, and intramuscular and subcutaneous injection), can now be performed with minimum risk in industrialised countries where specially designed equipment is available to minimise risks of PE.

Cost is an important constraint in acquiring the new range of products which are not standardised and which are substantially more expensive than the previously available equipment. Furthermore health care workers may need further training if new equipment is introduced, and supply of new equipment must be ensured. For example, using vacutainers to take venous blood samples has been designed to reduce the incidence of needle stick injuries, but supplying these intermittently to a rural African hospital without teaching nursing staff how to use them will be of no benefit.

The policy regarding protective equipment is one of the new aspects of a global strategy of protection of health workers in institutions. It is multidisciplinary and involves doctors, the administration, pharmacists, nurses, paramedics and laboratory staff. An infectious diseases control committee with authority to report incidents and decide on appropriate action for protection against nosocomial infection could be established. This streamlines and focuses activities and allows pooling of resources and expertise, and follow up of activities. The choice and use of protective equipment cannot be made without local evaluation and follow up.

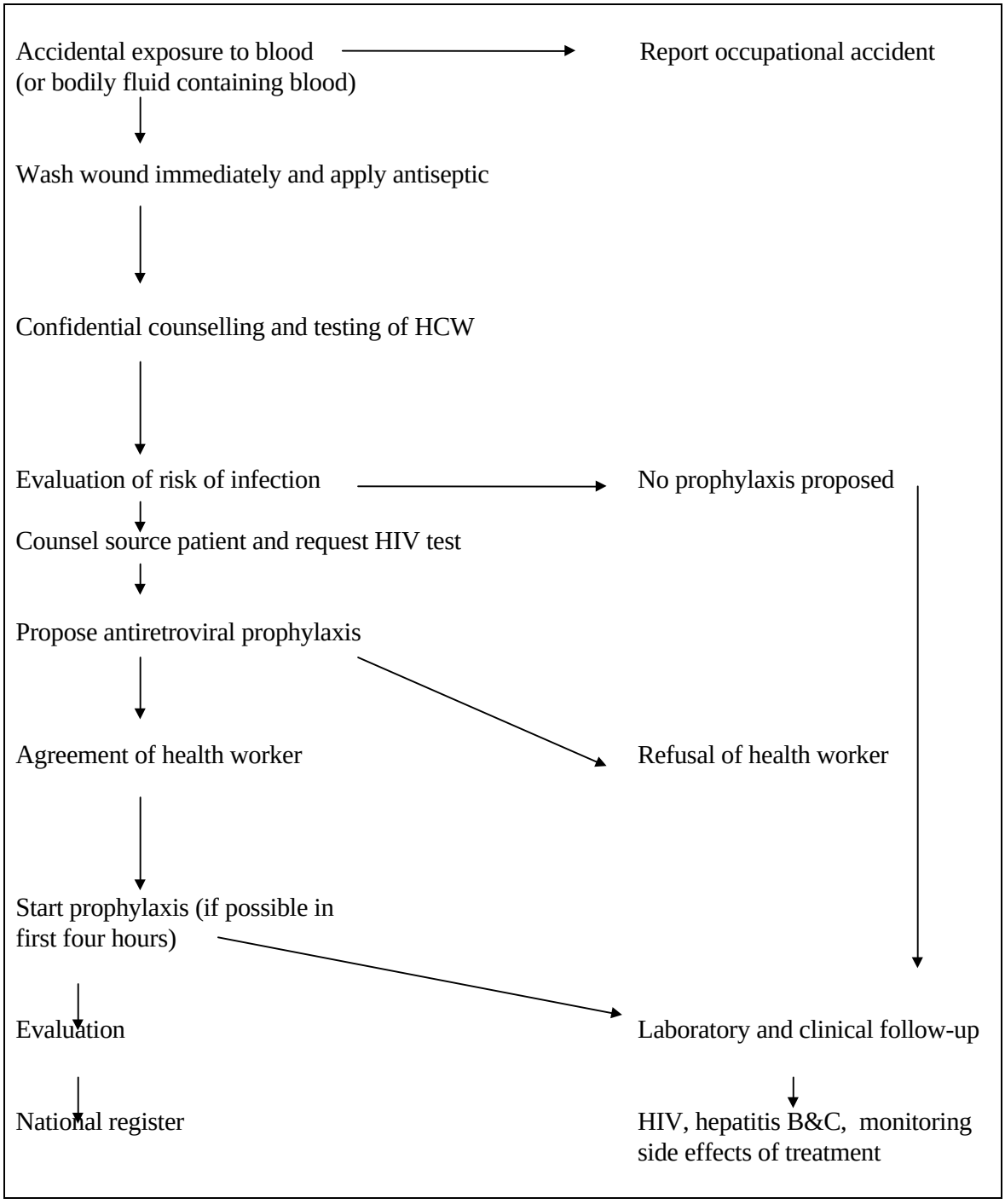
Training of Health Care Workers (HCWs) in universal precautions and prevention of AEB

All health workers and professionals at risk of exposure (nurses, doctors, laboratory technicians, nursing auxiliaries and surgeons) must be trained in prevention of AEB during the period of their studies rather than when they have started work. Health care workers (HCWs) at risk should have “refresher” courses to update their knowledge and should regularly review procedures as a team. The training should include organisation of care, analysis of accidents and training in the use of new safety equipment. Different training is needed for different categories of HCWs. In many developing countries although HCWs are aware of UPs they are unable to apply them because of shortages of basic equipment such as gloves and other protective clothing. In a study from Zambia a large urban hospital had few sharps boxes available and needles were sometimes thrown away with the general hospital waste or in cardboard boxes. HCWs need to find ways to improvise using the available resources. In high prevalence areas, many HCWs may already be anxious about HIV and may have had previous needle stick injuries. These anxieties must be addressed sensitively and counselling should be made available.

Register of AEB

Surveillance of AEB provides the foundation for all other activities - the design and setting up of policies and equipment, the application of universal precautions, and the training undertaken in institutions. Monitoring rates of AEB provides a measure for assessing the effectiveness of the different protective measures that have been introduced. For this it is important that AEB be reported in a standard way allowing observation of trends and evaluation of the impact of the measures taken. A standard surveillance register at national level would be useful and each institution should participate in the formulation of a concerted prevention policy. Confidentiality of HCWs who have been exposed to AEB must always be ensured. In some high prevalence areas, HCWs may be reluctant to disclose occupational exposure because of fear of stigmatisation.

Procedures in case of exposure



After first aid (washing wound and application of appropriate antiseptic), the next step is to provide counselling for the exposed HCW and evaluate the risk. Immediately after the accident, a doctor or other designated HCW should evaluate the severity of the exposure, taking into account the depth of the wound, the type of instrument involved, the bodily fluid and the serological status of the source patient, if known. The option to use PEP depends on the availability of ARVs. In the majority of industrialised countries, all AEBs, where the source

patient is known to be HIV infected or at high risk for HIV infection, are considered for ARV PEP. In some middle income countries, the recommendations apply only to serious accidents. Currently, in many developing countries no ARVs are available for PEP.

If ARVs are available, the next step will include determining the serological status and stage of illness of the source patient. It should be possible to carry out this evaluation (which determines the choice of treatment) 24 hours a day. The emergency services of the institution, therefore, should play an important role in the organisation of these activities.

Following the evaluation, the doctor, or designated HCW, may recommend or propose prophylaxis. The health worker may have considerable anxiety following the AEB and sensitive confidential counselling should be available. The exposed health worker should be informed about any uncertainties relating to the effectiveness of the treatment and the possible side effects. It is up to her/him to accept or reject the prophylaxis.

The indications for prophylaxis according to the severity of the cutaneous-mucosal exposure when the serological status of the source patient is known, are summarised below:

Type of exposure	**Source patient HIV seropositive**	
	Symptomatic and/or high viral load	Asymptomatic and/or low viral load
• Massive • Intermediate • Minimal	Recommended Recommended Possible	Recommended Possible Possible (but to be discussed)

Essential steps

Identification of the accident: the accidental exposure to blood must be recognised as such by the health worker. This requires training of persons at risk, care and non care providers.

Foresee/prepare arrangements: these should function 24 hours a day: anyone exposed should be able to receive confidential counselling and treatment in the hours following the accident.

Identify resource persons: among the hospital personnel to help the exposed person to take the necessary steps and take care of him/her.

Identify prescriber: to evaluate the risk, decide on treatment to be offered and follow up the patient.

Initial serology: The health worker who has been accidentally exposed should have HIV pre-test counselling and a reference serology within eight days of the accident to check for prior infection (this can be a frequent finding in high prevalence areas). All those initially testing negative should have follow up serology.

Serological follow up: counselling and testing should be offered at three and six months after the accident.

Provision of treatment: the drug treatment, which will comprise 1 or a combination of 2 or 3 ARVs must be available at all times, must not be out of date, and must be prescribed by a professional.

Serological testing of the source patient: when the serological status of the source patient is not known, this person must be informed about the accident in order to obtain consent to test for HIV antibodies. Confidentiality of the results must be the rule. If he/she refuses or consent is not possible (patient unconscious), prophylaxis should be considered if there are indications of possible infection (prevalence of infection among the patients in the institution, suspicion of a risk factor in the source patient).

Note that not all patients with risk factors are infected, and that in high prevalence areas, the concept of risk factors may not be very useful.

Therapeutic protocol after occupational exposure

The therapeutic protocol comprises three important elements:

- Timing of initiation of treatment
- Therapeutic regimen
- Laboratory monitoring.

Timing of initiation of treatment

Animal studies show that prophylaxis after exposure can definitively prevent infection if it is administered in a sufficiently short time (within eight hours with the most powerful drugs in

macaques). The maximum delay in initiation of treatment which would block infection is not known in humans. As the objective of post exposure prophylaxis is to prevent infection and not to treat an eventual primary infection, the time between exposure and initiation of treatment should be as short as possible. In most industrialised countries which have made recommendations, the optimal delay is extremely short, 2-4 hours. However, with the exception of Denmark which recommends a maximum delay of 24 hours to start treatment, there is no time limit in most country recommendations. Prophylaxis is sometimes given empirically up to 2 weeks in the case of severe exposure when the delay has been unavoidable.

Therapeutic regimen

The therapeutic regimen will be decided principally on the basis of drugs previously taken by the source patient and known or possible cross resistance to different drugs. It may also be determined by the seriousness of the exposure and the availability of the various ARVs in that particular setting.

So far, ZDV is the only regimen for which data on efficacy exist. However, double and triple therapy are now being used for PEP on an empirical basis in industrialised countries. The use of ZDV as monotherapy for PEP no longer appears justified in countries where it has been used in patients for 10 years, as its effectiveness may be reduced by the existence of resistant strains.

In most industrialised countries, the latest published recommendations tend towards bitherapy, using ZDV, the only drug that has been shown effective for this purpose, and another nucleoside reverse transcriptase inhibitor (NRTI), usually lamivudine, in order to increase antiretroviral activity and eliminate ZDV-resistant strains. Protease inhibitors (PIs) have not yet been tested for this indication, however, they are included in the therapeutic regimen in certain cases notably when the risk of transmission appears higher (severe exposure and high viral load in source patient). Their high therapeutic efficacy must be weighed against the risk of side effects. Drug interactions may also pose a problem. Some countries systematically propose tritherapy.

The combination and the recommended doses, in the absence of known resistance to ZDV or lamivudine in the source patient are:

- ZDV 250-300 mg twice a day
- Lamivudine 150 mg twice a day
- The PI recommended on the basis of its acceptable tolerance and limited drug interactions is indinavir 800 mg 3 times a day.

In developing countries where ARVs are not widely used and the source patients are therefore likely to be ARV naive, ZDV monotherapy for PEP is a valid option.

The recommended duration of treatment is four weeks, based on the results of the CDC case control study. However, the optimal duration has never been evaluated. Certain countries propose minimum treatment of two weeks and maximum four weeks.

Accidental exposure to blood for a health worker who is pregnant poses a particular problem, as data on ZDV tolerance in pregnancy in the first trimester is limited. Lamivudine, alone or in

combination with ZDV, has been tested in infected pregnant women, and shows good tolerance and a good placental diffusion with cord concentrations equivalent to maternal blood concentrations. A trial of tritherapy with ZDV/lamivudine/ritonavir as PEP is being developed. These agents present no embryotoxicity nor teratogenicity in animals and pass the placental barrier well. However, when prescribing in late pregnancy there is a theoretical risk in the child of neonatal hyperbilirubinemia and renal stones.

Current recommendations for the pregnant woman are in favour of nucleoside bitherapy if the accident occurs after the second trimester of pregnancy. If the accident occurs during the first trimester, the risk/benefit for the mother and the foetus (risk of treatment against risk of transmission) must be assessed on a case by case basis.

Serological and clinical monitoring

Serological follow up particularly for medico-legal reasons, requires testing for HIV antibodies at the time of the accident. Laboratory tests should include, at the minimum, a second HIV serology done three months after the exposure, when the majority of those who are infected have seroconverted. Beyond this, the risk of contamination by some other mode of transmission is higher and serological follow up no longer makes sense. However, currently published recommendations suggest a third serology, usually done at six months following the exposure, for those who have tested negative.

Initial laboratory tests should include (according to the treatment prescribed), blood count, renal and hepatic function, serology for hepatitis B and C (if these are available) and if necessary a pregnancy test. The minimum laboratory tests for monitoring undesirable side effects must include an FBC and transaminases. The pregnancy test is to take into account complications which may arise if the exposed health worker is pregnant.

The health worker taking PEP should be followed clinically during the treatment, especially to monitor side effects which might make a change in treatment necessary. The health worker must be informed about signs of primary HIV infection, so that he/she will be able to consult the doctor quickly.

Counselling following AEB

Counselling for prevention of transmission (safer sex, no blood donation etc.) whilst waiting for the follow up serology, should be provided to the health worker. The health worker may have anxieties about telling his/her sexual partner about the AEB and recommendations to use safer sex until the follow up test result is known. The health worker may wish to involve his/her partner in the counselling. Although PEP is highly effective and the risk of transmission post exposure is low, long term counselling and support services, possibly including treatment for HIV disease, must be in place for health workers who acquire HIV despite PEP. Whether ARVs will be offered to HCWs who acquire HIV despite PEP will have to be decided. If there is a national or hospital policy for compensation of HCWs for occupational injuries or accidents, accidental exposure to HIV may need to be included in this.

HIV testing of health care workers following AEB in high prevalence areas

In countries with the highest risk of acquiring HIV from AEB the background HIV seroprevalence rates amongst HCWs will also be high, irrespective of any occupational risk. Studies from sub-Saharan Africa have shown similar levels of HIV among health care workers as in the general population. Thus many HCWs will be seropositive at the time of the AEB. In studies among HCW at the University Teaching Hospital in Lusaka, Zambia, the majority of HCWs did not report AEB because they felt that they may already be infected - either by previous AEB or through previous sexual contact. Many said they did not want to know their HIV status, because if they were found to be seropositive there was little that could be done to help them medically, they feared rejection by their partners and they did not believe that the results would remain confidential. Confidential voluntary counselling and testing services in high prevalence areas need to be established for *all* HCWs. This service must be in place before considering introducing ARV treatment for PEP.

Evaluation

Evaluation of PEP, in particular with respect to acceptability, adherence, tolerance, and effectiveness is important as there is still much uncertainty about the efficacy and safety of PEP with ARVs for this indication. Thus it is important that physicians, and HCWs caring for exposed HCWs keep careful records of this data.

Records must include a detailed description of the accident, date, place, time, circumstances, type of exposure, severity, nature of the bodily fluids and the action taken: advice, risk evaluation, treatment and clinical and laboratory follow up. These data must be collected respecting the confidentiality of the exposed HCW and that of the source patient.

National treatment policies on occupational exposure to HIV

The CDC case control study that showed the efficacy of PEP with ARVs, led public health authorities in several industrialised countries to issue recommendations for policies and procedures following accidental exposure of health workers to HIV.

Comparison of national recommendations for prevention of infection after occupational exposure to HIV

Country	Definition of exposure	Time limit for start of treatment	Therapeutic combinations	Length in weeks	References
Germany	serious exposures	within 2 hours, no upper limit	ZDV/3TC/IDV	2wks min. 4 wks optimum	Epid.Bull. Oct.1996, updated Nov.97
Australia	1) percutaneous exposure 2) high risk or ZDV-resist.	within 2 hrs	1) ZDV,DDI or DDC and 3TC 2)2 nucleosides and PI*	6 wks	ANCA,Bull. No.16,March 96
Canada/ Quebec	1) percutaneous exposure 2) high viral load, patient treated with nucleosides, serious nature	within 2 hrs, no upper limit	1) ZDV/3TC 2) ZDV/3TC/ IDV	4 wks	CCDR March 19 97 updated Oct. 97
Denmark	percutaneous exposure	within 24 hrs max.	ZDV/3TC/ IDV	4 wks	awaiting publication
Spain	1) percutaneous exposure 2) high risk	a.s.a.p, no upper limit	1) ZDV/3TC 2) ZDV/3TC/ IDV	2 or 3 wks	CNS Nov. 96 updated Nov. 97
USA	1) percutaneous exposure 2) serious nature, resistance in source patient	within 2 hrs, no upper limit	1) ZDV/3TC or D4T 2) ZDV/3TC/ PI*	4 wks	MMWR 96, updated Oct.97
France	1)percutaneous exposure 2) serious nature, resistance in source patient	within 4 hrs, no upper limit	1) ZDV/3TC 2) ZDV/3TC/ IDV	4 wks	BEH Dec. 96
Netherlands	exposure to blood	within 2 wks	ZDV/3TC/IDV	4 wks	LCI June 1997
United Kingdom	percutaneous or mucosal, skin broken with blood or high-risk fluid	a.s.a.p	1) ZDV/3TC 2) ZDV/3TC/ IDV	2 wks min. 4wks max.	SFOPH February 1997
Switzerland	1) superficial wound or mucosal 2) percutaneous, HIV+ blood transfusion, accidental injection of contaminated fluid	a.s.a.p	1) ZDV/3TC 2) ZDV/3TC/IDV	2 wks min. 4 wks max.	SFOP February 97

*PI : protease inhibitor

Provision of chemoprophylactic therapy should be considered in countries and institutions where universal precautions have been successfully implemented. A programme of PEP implies that most accidents are avoided and UPs are practised. If protective clothing and "barrier" precautions such as gloves, have been used, the inoculum will have been reduced and PEP will be all the more effective. Furthermore, effective prophylaxis requires efficient organisation and management of AEB. The correct timing of treatment and appropriate choice of drugs are absolute imperatives for efficacy. The efficacy of the prophylaxis is not 100% and it is expensive, difficult to take and requires sophisticated health care facilities. It should therefore be considered in institutions where the other elements of a comprehensive prevention strategy of AEB are in place and functioning efficiently.

It should be noted that PEP with ARVs plays no role in the prevention of infection by hepatitis B or C; and the risk of transmission of these viruses is much higher than for HIV. Vaccination of HCWs against hepatitis B should be strongly recommended.

Therapeutic management of AEBs will also depend on the resources of the country and particularly on access to ARVs. There are strong ethical arguments for reserving part of this stock of ARVs for health workers in case of accidental exposure. In caring for HIV-infected patients, health workers are exposing themselves to risk over and above that faced by the general population. Making PEP available to them would contribute to making work in care units where HIV prevalence is high and safety measures less than optimal, more acceptable. However, the provision of counselling and testing services must be assured.

In countries where universal precautions are widely used and ARVs are available, it is imperative to set up a system in all hospitals allowing all workers to benefit from ARV treatment as rapidly as possible if the risk of transmission is considered significant. This would bring procedures into line with legislation on the obligations of employers to ensure the safety of employees at work and to compensate them for the consequences of work accidents.

The regimen offered could be bitherapy if resources permit or monotherapy with ZDV if it has not yet been widely prescribed in the country. It is recommended that the duration of treatment with bitherapy should be at least two weeks and four weeks with ZDV monotherapy. A register of exposed and treated health workers in large institutions in high prevalence areas would provide data for the evaluation of the management of accidental exposures to blood.

Cost estimates

The estimation of the costs of PEP should include:

- drug costs
- HIV testing costs (of exposed person & source patient)
- counselling costs (of exposed person & source patient)
- clinical monitoring, including follow up and treatment of adverse effects
- serological follow up over 3-6 month

Clinical care and time spent on counselling and testing and clinic visits by the exposed health care worker should be considered as well. Counselling services for health care workers may need to be set up.

Cost effectiveness estimations for PEP have been made in industrialised country settings[2]. These show the cost per case of HIV averted in the US is very high. However there are very strong arguments, beyond the economic ones, for offering protection to health care workers (see Module 9 on ethical and societal issues relating to ARV treatment for detailed discussion)

Cost effectiveness has been estimated based on the **total numbers** of PE with HIV contaminated blood. No distinction has been made between "massive" "intermediate" or "minimal" exposures. If all PE with HIV contaminated blood are treated with PEP it must be noted that 997 people out of 1000 will receive ARVs unnecessarily. If a more selective analysis of PE is made and only "massive" and "intermediate" PEs receive ARVs this will cut down the costs of the service and the numbers of people receiving ARVs unnecessarily. However their may be a very small minority of people in the "minimal" group for whom ARVs would have prevented transmission.

It is also important to emphasise that "cost effectiveness" estimations are only one of the considerations to be examined when setting priorities for ARV PEP. Ethical and individual considerations will often be of at least equal importance.

Prophylaxis after non-occupational exposure to HIV

ARV prophylaxis after non-occupational exposure to HIV is of concern to those who have had a sexual or parenteral exposure through sharing drug injecting equipment to HIV. This subject has only recently received attention, following new understanding of the pathophysiology of HIV infection, therapeutic advances with ARVs and evidence that ZDV is effective in PEP. Public demands have been made for PEP following non-occupational exposure. Although there are no consensus guidelines some practitioners in industrialised countries are prescribing ARV prophylaxis treatment after non-occupational exposure.

There are a number of **scientific arguments** to support prophylaxis following non-occupational exposure to HIV:

- Parallel immunological mechanisms exist for percutaneous and mucusal exposure;
- Similar rates of infectivity by each contact for the different type of exposure: percutaneous, mucosal or parenteral;
- Positive results of ARV trials in animals in cases of parenteral or mucosal inoculation as well as results of prophylaxis in pregnant women and health personnel;
- Availability of more powerful treatments than ZDV monotherapy.

Only the city of San Francisco (USA) and France have set up mechanisms to provide ARVs for non-occupational exposures. The treatment for non-occupational PEP draws on the protocol for health workers, with the difference that an upper limit on initiation of treatment is put at 48 to 72 hours.

The implementation of such a programme presupposes a certain number of conditions such as high prevalence of preventive behaviours; organisation of care and counselling allowing urgent

[2] Pinkerton S Cost effectiveness of chemoprophylaxis after occupational exposure to HIV Arch Intern Med 157 1972-80 (1997)

treatment of accidental exposure, the risk of which can be correctly evaluated, as well as follow up of patients; wide access to testing; availability of ARVs and proper evaluation of the programme.

Such a programme has only been implemented in industrialised countries with relatively low HIV seroprevalence rates. In such settings the number of “accidents” is low and the cost of treatment affordable. In a high prevalence country like Zambia (HIV seroprevalence amongst sexually active adults: 30%; number of condoms sold per annum approximately: 5 million; 1% breakage; 50,000 accidents) PEP following such “accidents” would be unaffordable. Clearly, for most countries in the world, treatment of non-occupational exposures cannot be considered a public health priority.

Rape

Whether people who have been raped should have access to ARV prophylaxis as a priority over those who believe they may have been exposed to HIV in consensual sex, either because of condom breakage or because of a failure to employ condoms during sexual intercourse, is a matter of debate. Those who claim that no distinction should be made between such individuals and rape victims wish to avoid the implication that the former are "guilty" while the latter are innocent. But proponents of treating rape victims preferentially make two arguments: First, the special claim of rape victims stems from the trauma to which they have been subjected. It may be argued that those placed at risk by consensual sex must assume responsibility for such risk (such as condom breakage) which any consenting adult assumes today in his or her sexual relations. Secondly, there is a fear that treating ARV prophylaxis as a "morning after" intervention may subvert prevention messages that stress the importance of practicing safer sex and the avoidance of unprotected sexual intercourse with those whose HIV status is unknown (See Module 9 on ethical and societal issues relating to antiretroviral treatments).

Conclusion

The availability of post exposure prophylaxis for occupational exposure does not replace traditional methods of prevention. It must be an integral part of primary prevention. It is justified only in situations where the wide application of prevention measures already reduces exposure to HIV. PEP should be viewed as an option when preventive measures have failed.

The average risk of infection after exposure to HIV is very low, compared to other infectious agents, such as hepatitis B and C. The average level of risk for a percutaneous exposure is around 3 per 1000. This low risk of transmission per exposure means that treatment is only useful for a minority of individuals exposed. This implies as accurate as possible an assessment of risk following the exposure, in order to avoid exposing individuals unnecessarily to a treatment, the toxicity of which is not yet known in healthy subjects.

Results from a case control study in humans and several animal trials indicate the efficacy of nucleoside monotherapy. This treatment has been shown to be effective when initiated rapidly after exposure but there are limited data on PEP given after 24 hours. In animals, efficacy decreases significantly with time. Efficacy is related to dose and duration of treatment. Currently published recommendations for treatment following exposure in humans are those established for health workers. Usually no time limit is placed on initiation of treatment,

although it is strongly recommended to start treatment in the first hours following exposure and to continue for four weeks.

Trials in animals combining several drugs, testing different timing of initiation, and durations of treatment less than four weeks, allowing better adherence and limiting secondary effects, are ongoing. Although short term side effects of treatment are very frequent, they are generally moderate, and reversible after stopping treatment. Exposure of a large number of healthy people are likely to reveal toxicities that are not yet known. So long term monitoring will be important. In industrialised countries where source patients are likely to be taking ARVs, bi- or tritherapy as PEP is usually indicated, whereas in developing countries where source patients are usually ARV naive, zidovudine monotherapy (ZDV) is recommended.

Treatment of HCWs after exposure to blood is appropriate in countries where training, prevention and surveillance of accidents in health care institutions are well organized. It is not a priority in countries where there are many avoidable AEBs as a result of inadequate protective material and equipment and insufficient training in prevention measures. Adequate training of HCWs and provision of HIV education and counselling to all HCWs must precede the introduction of ARV PEP services.

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

For orders, contact:
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email: unaids@unaids.org

Office of AIDS and Sexually Transmitted Diseases (ASD)
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Module 8
Antiretrovirals: Regulation, Distribution and Control

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Acknowledgements

The World Health Organization and UNAIDS would like to thank Ms Pascale Brudon, and Ms Muriel Dubreuil, Action Programme on Essential Drugs, WHO, for preparing the text of this module;

Dr Richard Laing, Boston University, Boston, USA, Dr Philippa Saunders, Essential Drugs Project, London, UK, and Dr Mary R. Couper, Drug Management and Policies, WHO, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for coordinating the project.

Module 8

ARVs: Regulation, Distribution, and Control

The objective of this module is to provide guidance to policy-makers and senior managers on the effective management of antiretrovirals (ARVs) so as to ensure their safety, efficacy, and quality from procurement to end-use. It is intended to provide support at two different points in time:

- Before a decision is made to introduce ARVs, the module can assist senior managers to check if minimum structures, systems and policies are in place and to evaluate additional resources and investment needed to make ARVs available, and ensure their rational use.
- Once the decision has been made to introduce specific ARV treatments for certain target groups, the module provides support in troubleshooting, improving the efficacy and reliability of the pharmaceutical system, and building a consistent and sustainable ARV supply.

1. Introduction

For many PLHA, ARVs represent the only hope and the best available treatment which may increase survival and quality of life. Understandably, obtaining ARVs is likely to be a major preoccupation of many PLHA all over the world. However, at government level, the decision to introduce ARVs is a complex one, as ARVs are very expensive, the treatment is difficult to adhere to, and requires efficiently functioning health and social services. Governments can decide not to permit the importation and use of ARVs in the country, or to permit the distribution of ARVs only in the private sector or to provide them through public health services. Individual countries need to analyse their own situation before making any decision. (See Modules 2 and 3 for further discussion of this issue).

When a government decides to introduce ARVs, a reliable and regular supply of good quality ARVs must be assured. For a variety of reasons, ARVs pose a particular challenge in this respect:

(1) The development of resistance is "just around the corner". It has been shown that minor lapses in adherence may lead to the development of resistance and thus interfere with efficacy.

(2) It is almost certain that given a treatment which is perceived as life saving, but that is very expensive, a black market will form; counterfeit and substandard drugs will start to circulate and a parallel drug supply system will operate.

The procurement, distribution and dispensing of ARVs require therefore functioning national quality assurance and supply systems. In the following pages, we will try to describe what should be done in developing countries to ensure that ARVs are of acceptable quality, are in continuous supply, and appropriately dispensed.

2. Characteristics of pharmaceutical systems

Measures in a particular country to ensure that ARVs are well controlled and managed are closely linked to the structure of its pharmaceutical sector, the capacity of the drug regulatory agency, the level of training of its personnel and its pharmaceutical pricing and financing policies.

In low income countries, health services are in general in a poor state; trained pharmacists are few especially in the public sector, drugs are supplied through public and private health facilities, pharmacies and drug outlets. Drug regulatory authorities have limited capacity to enforce legislation and regulations. Expenditure on drugs is low (between 1 and 10 US$ per capita) and mainly financed directly by households. Shortages of essential drugs in public health facilities are common and prices in the private sector are unaffordable for the majority. These countries face major problems when introducing ARVs as the minimum conditions required to ensure their rational use cannot be met. However, in a number of countries ARVs are already available in private pharmacies. The extent of the problems, which include black markets, is not yet well known.

In middle income countries, health services are often better organized; drugs are supplied by public and private providers (pharmacies and drug outlets); the regulatory capacity of governments tends to be greater; pharmaceutical expenditures are higher in absolute terms with a higher proportion of public financing and still a large out of pocket share. However, in many middle income countries drug supplies in the public sector are uneven; financial access remains a problem; regulations are poorly enforced; and irrational use of drugs is rampant. In these countries, a variety of ARV dispensing strategies are in place which are closely linked to ARV financing strategies. In Brazil, for example, ARVs are fully subsidized and available free to HIV-positive individuals from the Unified Health System through governmental health services, whereas in Thailand, people with HIV/AIDS are included in a network for clinical trials in selected hospitals. In South Africa, on the other hand, there is no public expenditure on ARVs.

In industrialized countries, health care coverage is almost universal, health care delivery systems are well organized; drugs are supplied by public and private providers (pharmacies); regulations are comprehensive and well enforced. Therefore, access to and quality of ARVs is a less important issue than in other countries. The main concern is how to ensure maximum adherence to treatment. The way distribution of ARVs is organized has an influence on this adherence. Distribution varies considerably according to the organization of public health systems: from dispensation restricted to hospital pharmacies, to “double dispensation” wherein the hospital pharmacy is responsible for initial prescribing with subsequent dispensing entrusted to private outlets, to dispensing by both hospital and private pharmacies.

In view of the wide disparities between countries, solutions to ensure availability of good quality ARVs have to be tailored to country characteristics. However, there are a number of minimum structures/systems/policies which need to be in place, before any ARVs are made available in a country.

The next chapters will highlight some of the challenges and the various measures, actions and procedures which are essential and which cannot be ignored by governments. These measures are the most important ones and should be considered as the bare minimum. Indeed the supply, distribution, and provision of ARVs require a national commitment to implementing quality assurance systems, keeping in mind that:

- Access to and use of ARVs must be integrated within a continuum of care comprising home, community, and hospitals.
- Non-discrimination and equity in access should be ensured for individuals in ARV target treatment groups.
- There must be a comprehensive policy on ARVs which should be part of the national drug policy and should be based on the concept of essential drugs.

3. Ensuring that ARVs are of acceptable quality

Many of the measures which are described in this chapter apply to all drugs. For example, a legal and administrative framework must be in place in all countries to regulate, and control the pharmaceutical sector in order to ensure that only drugs of acceptable quality are available. However, these measures are particularly important for ARVs as the presence of substandard or counterfeit ARV can lead to a number of problems.

Risks of low quality ARVs:

- Therapeutic failure
- Development of resistant strains
- Health threats (toxic or adverse reactions)
- Waste of already meager resources

Maintaining quality of ARVs during procurement

In most developing countries ARVs will be procured from outside and not produced in the country. Whatever the situation is, it is important to use some simple procedures to ensure that ARVs conform to acceptable standards of quality, safety and efficacy when procured. These procedures apply for ARVs distributed in the public or in the private sector.

- **Register ARVs:**

  Even in least developed countries where the drug regulatory authority has limited capacity, the Ministry of Health should ensure that a product license has been granted by the drug regulatory authority before allowing any pharmaceuticals, including ARVs, into the country.

Small regulatory authorities do not have the capacity to undertake the multidisciplinary assessment needed for ARVs, they should therefore rely primarily on information provided by well developed national drug regulatory authorities; this can be done on a country to country basis or through the network of national information officers established by WHO.

Where no formal system of drug licensing has been established, importation of ARVs can be most effectively controlled by issuing permits in the name of the drug regulatory authority to the authorized importing agency.

- **Make full use of the WHO Certification Scheme on the Quality of Pharmaceuticals Products Moving in International Commerce:**

  This scheme constitutes a formal agreement between participating Member States to provide information on any product, notably on its registration status in the country of origin and whether or not the manufacturer complies with WHO's guidelines on good manufacturing practices (GMP) for pharmaceutical products.

- **License importing agents and distributors:**

  All transactions relating to the importation of pharmaceutical products including ARVs should be conducted either through the government drug procurement agency or through independent importing agents and distributors specifically designated and licensed by the national drug regulatory authority.

- **Deal directly with ARV manufacturers:**

  This allows for checking the exporting source and buying only from known ARV suppliers (all ARVs are single-source drugs).

- **Include detailed product specifications in drug procurement contracts:**

  - Indicate accepted pharmacopoeia standards when they exist.
  - At time of delivery, at least two years or 75% of shelf life should remain to avoid early expiry.
  - Contract terms should require standard labelling and proper packaging of ARVs.

Maintaining the quality of ARVs during importation

The WHO Scheme and the above mechanisms need to be complemented by administrative and other safeguards aimed at ensuring that consignments of imported ARVs are in conformity with the import license. All formalities undertaken on importation should be coordinated by the customs service which need to work closely with the drug regulatory authority. It is therefore extremely important to have a well functioning drug inspection system and to use the most trained personnel for the activities related to importation and distribution of ARVs.

Most important measures include:

- **Require key documents from the importer before customs clearance:**

  - Certified documents attesting that the importer is duly authorized by license to undertake the transaction..
  - A batch certificate issued by the manufacturer in line with the requirements of the WHO Certification Scheme.

- **Specify designated customs posts.**

- **Carry out effective control at specified entry points:**

  - *Inspection:* visual and physical examination checking for compliance with the contract conditions concerning drug type, quantity, presentation, packaging, labeling, and any special requirements, and reporting of suspect products.
  - *Routine sampling and independent drug analysis* to validate product content and drug concentration, in case the product has deteriorated, or is of doubtful authenticity. If no facility exists at national level, organizing quality control with outside laboratories may be a solution.

- **Formulate and supplement procedures for donations of ARVs:**

  - Use the guidelines for Drug Donations developed by WHO and other agencies (WHO/DAP/96.2) to define national guidelines for donations of ARVs
  - Define administrative procedures for receiving donations of ARVs.
  - Define administrative procedures for receiving donations of ARVs.
  - Specify the needs for ARVs (in terms of the kind of drugs and the quantities).
  - Manage ARVs donations as other ARVs.

Maintaining the quality of ARVs through the distribution chain

The ARVs should remain secure within the distribution chain. This distribution can be done by the government procurement agency or by private wholesalers; the precautions are the same in the two channels and are basically the same as for other pharmaceuticals. However, as ARVs have a number of characteristics described above, it is advisable in countries with limited resources to give more attention to the management of these drugs at all levels of the chain.

Most important measures include:

- **Appropriate transportation and storage conditions:**

  Ensure compliance with maximum allowable temperatures. During transportation the maximum temperature for most of the ARVs is +30°C; it is only +8°C for Ritonavir. The same applies for storage: Ritonavir should be kept in a refrigerator set between +2°C and +8°C; the other ARVs can be stored in dry, clean, well ventilated storerooms maintained between +15°C and +25°C.

- **Special attention to the management of ARVs:**

  Distributors whether public or private should have reliable records of ARV stocks and in certain cases keep ARVs in a separate locked area. In addition, the most experienced and competent staff should be made aware of the specific importance of ARVs and assigned the task of supervising the ARV distribution chain.

  At dispensing level, consumption reports showing the time, date, patient, dose, and remaining stock levels should be kept by the hospital pharmacy.

Essential measures to ensure quality of ARVs:

- Allow only registered ARVs on the market.
- Allow only licensed importers to import ARVs.
- Use the WHO Certification Scheme.
- Designate customs posts for importation of ARVs.
- Physically inspect all consignments.
- Respect transportation and storage conditions for ARVs.
- Give special attention to the management of ARVs at all levels of the distribution chain (inventory control, storage, etc.).

4. Ensuring a continuous supply of ARVs

Ensuring a continuous supply of ARVs is a key issue in the management of ARVs. Adherence is particularly critical in relation to ARV treatments. There is evidence of drug

resistance resulting from minor lapses in adherence. Many factors influence adherence to treatment and obviously, unreliable supply is one of them. Unreliable supply may be due to problems in financing ARVs (discussed in Module 2) or to poor drug management.

Risks of unreliable supply and distribution of ARVs:

- Decreasing treatment efficacy or treatment failure
- Increasing risks of emergence of resistance
- Compromising patients' commitment to adherence
- Demotivating health professionals
- Increasing unregulated supply and distribution of ARVs

National systems vary with respect to public and private roles in procuring, distributing, and dispensing drugs. In organizing the supply of ARVs, governments can:

- Assume the responsibility to provide publicly-funded ARVs
- Leave the financing and supply of ARVs to the private market
- Develop a combined public/private supply strategy.

Regardless of the approach selected, public health authorities must make sure that there is no shortage of ARVs at the agreed points of dispensing.

ARV supply management

- **Develop group purchasing:**

  Regardless of how the drug supply system is organized, a centralized procurement system in which one procurement office, whether publicly or privately managed, negotiates ARV supply contracts, offers several potential advantages:

  - Larger procurement volume, even for single-source drugs, creates the conditions for reduced prices and favourable contract terms.
  - With only one procurement unit to staff and manage, it is easier to maintain the rational procurement of ARVs and a constant supply to distributors, thereby ensuring the sustainability of the programme. This centralized procurement system can cover the provision of ARVs for the public and the private sector.

- **Calculate ARV requirements carefully:**

  ARV orders should be based on reliable estimates of actual need so as to avoid stock-outs or overstocks (AIDS pattern, morbidity data, consumption records).

- **Specify divided ARV deliveries in terms of contract:**

  Even when ARVs are ordered only once a year, divided deliveries allow reductions in inventory holding costs, ease cash flow constraints, and result in increased ARV shelf life.

Distribution of ARVs through the public sector

Deciding to provide ARVs through the national public health system implies a commitment to guarantee a regular and long-term supply to a number of dispensing points. Public health authorities have two options for achieving these demanding objectives: integrating ARV distribution into the existing drug distribution system or creating a specific distribution for ARVs. The choice must be made after a careful assessment of the existing drug supply system, with the long term goal of an integrated drug distribution system.

- **Integrated distribution:**

  The relative strength and weakness of current distribution systems can be assessed by using some simple key indicators such as percentage of inventory variation in stock record-keeping, percentage of expired drugs in stock, stock-out frequency for indicator drugs or delivery delay at different levels of the distribution chain. Relevant activities aimed at redesigning the existing system can then be planned, in line with the following objectives:

  - Maintaining a constant supply of ARVs.
  - Ensuring the timely delivery of ARVs to chosen dispensaries.
  - Ensuring that ARVs are properly stored, with minimal expiration or other losses.

- **Vertical distribution:**

  If the existing national distribution system is ineffective, implementing an ARV-specific distribution system -- which implies mobilizing new resources and establishing a new management structure -- can be a temporary alternative, particularly initially, where only a few distribution points have been identified. Designing a new organization allows for planning ARV distribution, setting up an efficient network of storage facilities with the fewest number of levels appropriate to the country's geography and ARV treatment needs, and achieving more rational use of transportation facilities.

Table 1: Integrated versus vertical distribution system		
System	**Advantages**	**Disadvantages**
Integrated	• Option of choice if chosen dispensary is easy to reach by existing distribution system • High quality requirements of ARV supply pulling forward the whole supply chain • Challenge of ARV introduction stimulating staff and helping changes in management • Less costly: use of existing resources	• Risk of disrupted supply and stock-outs when there are structural weaknesses in the system • Difficult to implement strict quality assurance procedures • Storage points may not suit the needs of ARV distribution
Vertical	• Establishment of central unit in MoH with overall responsibility • Long-term planning, coordination, supervision, and monitoring of ARV supply facilitated • Easier to prevent unexpected events • Homogeneity of quality assurance procedures • Reliable information system for coordinating distribution network easier to implement	• Higher management costs • Developing a new vertical programme for ARV supply is not a rational measure in countries where a national drug procurement and distribution system exists

Dispensing

Selecting where to deliver ARVs is closely linked to who is to receive antiretroviral therapy. Choosing dispensaries is also conditioned by several other factors:

- ARV financing strategies
- HIV/AIDS prevalence in the country
- Selected target group (PEP (post exposure prophylaxis), MTCT (mother to child transmission), AIDS, HIV patients)
- Need to monitor efficacy and toxicity of ARV treatments.

Based on these factors and the existing situation in the country, governments will decide that ARVs will be available in the public, in the private or in the two sectors.

- **Dispensing through public health services:**

  When deciding where ARVs should be dispensed, the following guidelines should be taken into consideration:

  - Conceding priority for ARV supply to existing facilities for AIDS medical care
  - Ensuring that chosen ARV dispensing facilities can be easily and regularly supplied (reliable transportation and scheduled deliveries)
  - Ensuring inclusion of retail points in clinical, laboratory, and social support network
  - Taking into account the educational levels of dispensing facilities' personnel
  - Involving pharmacists in multidisciplinary teams of ARV therapy monitoring
  - Guaranteeing joint and convenient access to dispensaries and laboratory facilities
  - Ensuring that targeted patients will be able to come to the same dispensing facility for follow-up purposes.

The main concern in choosing the adequate level for dispensing facilities is their degree of technical expertise and specialization. Since full coverage is not currently achievable in most countries, one approach might be to ensure access to ARVs in a limited number of facilities where clinical, laboratory, and social support can be guaranteed.

The pros and cons of centralized and decentralized ARV dispensing level are listed in the following table.

Table 2: Centralized versus decentralized ARVs dispensing		
Dispensing level	**Advantages**	**Disadvantages**
Specialized (regional level) • Selected centres • Hospital pharmacies	• Close relationship with hospital clinicians • Hospital pharmacists' expertise • Faster and safer ARV supply • Easier ARV quality monitoring • ARV adverse reactions surveillance and reporting facilitated (team monitoring) • Easier constitution of a therapeutic file for treatment monitoring • Training workshops easier to implement (key staff from provincial hospitals, for instance) • Regular updating of treatment standards and recommendations facilitated (know-how of a few specialists)	• Decreased ease of access • Difficult for community to participate in ARV therapy supervision
Decentralized (district level) • Hospitals • Health centres	• Better equity in access • Use of local social and familial resources to ensure treatment adherence and follow-up • Possible to integrate with TB care systems	• Lack of available human resources and local infrastructure, lack of expertise and suitably trained staff • Increased costs of distribution • Risk of decreasing ARV quality • Increased risk of thefts • ARV treatment supervision more difficult; increased risk of inappropriate use, bad compliance, and resistant strains emergence • ARV adverse reactions monitoring limited

- **Dispensing through private pharmacies:**

  Governments may decide to allow ARVs to be sold in the private sector, considering that patients with sufficient disposable income have the right to obtain these therapies. Governments should be aware that regulations and their enforcement are very important to ensure that ARVs are distributed appropriately in the private sector. This means that the system for regulatory drug control including inspection and drug quality laboratory has to function properly. Ideally the same principles as for dispensing in public health services should be adhered to. In addition:

  - Limitations should be placed on the number of drug outlets allowed to sell ARVs in a given town or district. The quality of ARVs sold by a few well known retailers is easier to monitor.
  - To protect patient health, it would be important that patients who buy their ARVs in the private sector do so only if the drugs have been prescribed by an authorized source and the treatment is monitored under strict medical, laboratory and care conditions in a designated centre.
  - Private outlets should be licensed for ARV sales only if located near clinical, laboratory, and social structures for treatment supervision.
  - Pharmacists should be trained in ARV dispensing; training sessions could be jointly organized by public health authorities and ARV producers.

Essential measures to ensure continuous supply of ARVs:

- Give special attention to the management of ARVs.
- Encourage group purchasing to reduce ARV prices.
- Assess the distribution system before deciding on an integrated or a vertical approach.
- Select carefully the places (public or private) where the ARVs will be dispensed to patients.
- Give special attention to the inspection/supervision of dispensing outlets.

5. Ensuring correct dispensation of ARVs

Dispensing ARVs correctly is an important step in ensuring adherence to treatment. Problems concerning ARVs do not end once these drugs become accessible. The counselling process at the dispensing point should be able to partly address the factors that adversely affect adherence.

Combination therapy is complicated. ARVs have to be taken many times a day. Some have unpleasant side effects which may become difficult to accept by the patient. When ARVs are dispensed in public health facilities, pharmacists are usually part of a team responsible for information on drug taking. When ARVs are dispensed in private pharmacies, they should be able to address issues which will maximize adherence to the treatments. This implies additional responsibilities for pharmacists.

Risk of incorrect dispensing of ARVs:

- **Incomplete or bad adherence to ARV treatments**
  - Less effective regimen, possibly leading to treatment failure
  - Development and transmission of ARV-resistant viral strains
  - Waste of valuable resources
- **Toxicity of ARV treatments (side effects and interactions)**

- **Pharmacists or other health staff involved in dispensing need to be trained to provide information and to improve their communication skills:**

Appropriate training is very important; the training should associate all health care providers dealing with HIV/AIDS and include issues related to information and to communication, including dealing with the stress which may occur in patients when drugs are not available or treatment has not been adhered to. This training can be organized at regular intervals and cover an increasing number of pharmacists and other personnel. Pharmacists also need to know where and when to refer patients for counselling.

- **ARVs should be issued to patients with clear instructions and advice:**

  - As far as possible, ARVs should be given directly to the named patient.
  - Every effort must be made to confirm that the patient understands the complexity and duration of ARV treatment (patients' commitment to ARV therapy).
  - Pharmacists should make sure that the patient understands the dosage and course of therapy. Advice should concentrate on when and how to take ARVs and how to store them.
  - Written or symbolic instructions could accompany ARVs (detailed timetable, pictograms, etc.).
  - Warnings about possible side effects should be provided.
  - Instructions should be organized: patients remember best the first instructions provided.

- **A personal relationship should be established with patients:**

- Need for confidentiality and privacy when explaining use of ARVs must be recognized.
- Adequate time should be devoted for ARV dispensing.
- Patients should be advised always to come to the same pharmacy.
- As far as possible, the same person from the pharmacy team should follow each patient.

Pharmacists should be able to answer all specific questions and problems encountered by patients related to ARV treatments (side effects, interactions, and so on) and refer to clinicians where appropriate.

- **Follow up of non-attenders should be arranged:**

  - Participation of NGOs, community groups, and consumer and professional organizations should be sought.
  - Regular meetings to motivate patients should be organized.

- **Patients self-monitoring should be developed:**

  - Involvement of close relatives.
  - Self-monitoring procedures to regularly and systematically evaluate treatment adherence should be implemented by mixed physician/pharmacist teams.

- **Follow-up the effects of ARV treatment:**

  Pharmacists, in collaboration with other health professionals, have a key role to play in following individual patients for adverse reactions and toxicity:

  - Pharmacists should recognize side-effects and interactions associated with ARV therapy, and be able to refer patients and inform physicians.
  - An individual therapeutic file for treatment monitoring should be constituted at the dispensing facility level to document and trace ARV treatment events for each patient. Details of ARVs dispensed must be entered into this file before being issued to patients (date, patient's name and age, drug name, dosage and amount issued, dispenser's name).

- **Health personnel should be alerted to the need to report adverse reactions:**

  In the medium term it is important for countries to report adverse reactions to ARVs; a system for reporting to a specific centre may be established step by step.

Essential measures to ensure good dispensing of ARVs:

- Train pharmacists in communication skills.
- Provide clear and simple instructions to patients on use of ARVs and adverse effects.
- Establish a relationship based on confidence between the patient and the pharmacist.
- Ensure through regulations that prescribing and dispensing of ARVs are limited to specific places and persons.
- Ensure that patients are followed by the same pharmacist when ARVs are available through private pharmacies.

6. Supporting activities

Prescribers, pharmacists, and patients must become acquainted with ARVs and learn to use them. They all require information and should not rely only on manufacturers' promotional information. When deciding to introduce ARVs into the health system, governments should consider ways to ensure that independent information is made available; this can be done through the AIDS programme or through the Drug Information Centre when these structures exist. Information should include data on updated recommendations and ARV treatment standards.

Introducing new therapeutics such as ARVs demands new skills and attitudes. This means that time must be devoted to providing training either in basic or continuing education programs. This training needs to be directed at different categories of personnel.

- **Inspection services:**

  Inspectors should be trained to promptly and accurately identify counterfeit or substandard ARVs. As in many countries the number of inspectors is very limited, it could be opportune at the beginning to select one or two and to provide them with a more intensive training on specific aspects of regulating ARVs.

- **Managers and operational staff:**

  Specific practices developed to manage ARVs should be taught to staff assigned to keep track of them.

- **Pharmacists:**

  The dispensers play a crucial role in ensuring patient adherence to ARVs therapy. The quality of dispensing may be affected by the training and supervision the dispenser has received and the drug information available to him or her.

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

Office of AIDS and Sexually Transmitted Diseases (ASD)
World Health Organization
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4613
Fax: 41 22 791 4834

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Guidance Modules on Antiretroviral Treatments

Module 9
Ethical and Societal Issues Relating to Antiretroviral Treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)

World Health Organization (WHO)

WHO/ASD/98.1
UNAIDS/98.7

Acknowledgements

The World Health Organization and UNAIDS would like to thank Dr Ronald Bayer, Columbia University School of Public Health, New York, USA for preparing the text of this module;

Dr George Browning, University of Glasgow, Scotland, UK, Dr Jonathan Mann, Harvard School of Public Health, USA, De Kevin De Cock, Centers for Disease Control and Prevention, Atlanta, USA, Father Michael Kelly, Kara Counselling and Training Trust, Lusaka, Zambia, Mr David Chipanta, Global Network of PLHA, Lusaka, Zambia and Mr David Patterson, Policy, Strategy and Research, UNAIDS, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriëns, Policy, Strategy and Research, UNAIDS, for coordinating the project.

The views expressed in these documents by named authors are solely the responsibility of those authors.

Module 9

Ethical and Societal Issues Relating to ARV Treatments

Introduction

Advances in the treatment of HIV-related disease made during the last two years mark what may be a fundamental change in the capacity to manage what had been considered a uniformly fatal condition. Following the Ninth International AIDS Conference in Berlin, where results of the Concorde zidovudine trial were presented, many expressed despair over finding a treatment for HIV-related disease. With the introduction of combination and antiretroviral treatment, hope has been renewed. In the advanced, industrialized nations, combination therapies (usually two nucleoside analogues and a protease inhibitor) have become the standard of care.

At the Eleventh International AIDS Conference in Vancouver, July 1996, researchers presented evidence suggesting the possibility of dramatically reducing the viral load of HIV-infected individuals with combination therapy using at least three ARVs. Such an achievement, it was suggested, could extend periods of symptom-free life and life expectancy. Subsequent clinical reports confirmed the dramatic impact of the new ARV therapies. There was speculation about the prospect of eradicating infection in those already carrying HIV. Unfortunately subsequent research has shown that this is very unlikely. However, the popular media in the USA and other economically advanced nations came close to declaring victory in the struggle against AIDS and this has dramatically altered perceptions about AIDS as a uniformly fatal disease.

Some have remained skeptical, recalling the ultimately unfounded enthusiasm for monotherapy with ZDV but for many clinicians and hundreds of thousands of their patients, a new era of treatment has begun.

Ethical challenges

The new sense of therapeutic efficacy has produced ethical challenges in both advanced industrial countries, and in resource-constrained countries where the vast proportion of people with HIV infection live.

Much discussion of health policy generally, and of the challenges posed by ARV therapy more specifically, centres on questions of fact: How much will new treatments cost? How much of gross domestic products or of health care budgets would be required to meet the needs of some or all who might benefit from therapy? What kind of assistance would be needed to make the provision of ARV therapy possible in resource-constrained countries and at what level? These are important questions which can be answered empirically. But as important are questions of ethics. What do nations owe to their citizens who are critically ill in terms of provision of health care and other social support? Is health care a right? And if it is a right, how extensive are its claims? How should the needs of those with HIV infection be balanced against those with other medical conditions? When insufficient resources are available for all to benefit from

ARV therapy, would it be acceptable for some to benefit? How should such selections be made? Do the wealthy nations have an obligation to assist less developed nations in gaining access to ARV therapy? If they do, what level of assistance would satisfy such an obligation?

Each of these questions presents decision makers with difficult choices about what ought to be done given available resources. These decisions must involve ethical considerations which, in turn, reflect deeply held moral conceptions of the obligations of nations to their citizens. Because decision makers, communities, health professionals and individual patients have different values, interests and responsibilities, these ethical choices may require difficult trade-offs. Thus, for example, a commitment to maximize equality will often require some compromise with a commitment to maximize liberty.

Different ethical questions for rich and poor nations

The new therapeutic advances are available and socially affordable only in the advanced industrial nations. In these nations, ethical questions will surface as governments must determine whether they will extend the benefits of ARV treatment to all who could benefit despite the high costs involved. Furthermore, it will be necessary to confront the question of whether concerns about viral resistance induced by poor adherence to complex regimens can justify a refusal to prescribe ARVs to those who request them. In short, in the industrialized nations the new ARVs will pose challenges to the principle of justice, which requires a fair distribution of health care services, and to the principle of autonomy, which requires respecting the preferences of individuals when those preferences do not impose burdens or harm on others. In poorer nations, the picture will be very different. The new therapies will be largely beyond reach, and decision makers will be required to determine how severely limited national resources can be used to fund continued HIV prevention efforts and the palliative care and social support of those suffering with advanced HIV disease. They will have to make difficult rationing decisions regarding access to ARVs in situations of extreme resource constraint.

In the end, the gulf between the therapeutic prospects in the wealthiest nations and the poorest nations will compel the global community to confront the question of what obligations exist across borders to assist those with HIV infection.

Antiretrovirals: the high cost of progress

The new combination therapies are costly by any standard. In the United States, the addition of protease inhibitors to the therapeutic armamentarium has tripled retail prescription costs of drugs used in treating HIV disease, bringing the average to US$10,000-$15,000 per year, per patient. The viral load assays necessary to monitor the drugs' effectiveness add further expense. In the USA, which, unlike other advanced industrial nations, does not have a national health insurance programme that covers all citizens, scientific progress represented by ARV combination therapy has compelled government officials to confront the limits of the patchwork of programmes designed to assure access to HIV-related services. Despite the rapid increase in funds for such purposes, many thousands of patients have been unable to afford treatment. The ethical challenges posed by such restrictions are fundamentally different from those that will confront policy makers and clinicians in nations where more than 90% of the world’s HIV infected people live.

It has been estimated that if all those who could benefit from such treatment were to receive it in Sub-Saharan Africa, Southeast Asia, and Latin America, at current prices for drugs, the cost would be US$ 101.9 - US$ 161.4 billion, US$ 57 - US$ 90.2 billion, and US$ 9.1 - US$ 14.4 billion respectively. To place these figures in context, the costs were compared to both total health expenditures and gross domestic product for each region. In Sub-Saharan Africa, the costs of ARV treatment would represent 1763% of current health expenditures and 66.9 % of gross domestic product. In Southeast Asia, the costs would represent 364% of total health expenditures and 14.6% of gross domestic product. For Latin America the costs would represent 23.9% of total health expenditure and 1% of gross domestic product.

These extraordinary and obviously unaffordable sums understate the case. They do not include the cost of critically important provision of treatment for opportunistic infections, palliative care for those who do not respond to the new treatments, and the costs of social and psychological support to those dealing with a burdensome disease, and a complex medical regimen.

Only a radical reduction in the price of drug therapy and massive assistance from the wealthiest nations of the world could begin to alter this grim picture.

Drug pricing

How should one consider the fairness of prices for therapeutic agents, and especially for drugs that may critically affect the life prospects of individuals afflicted with a fatal disease? Advocates of a market approach assert that regulation of prices is not only unnecessary but would be counterproductive. "The basic principle governing the free enterprise system is that free and unrestrained competition should force fair prices. The more segmented the industry, the truer that is, and the pharmaceutical industry...is highly competitive." Those who reject the market as the sole arbiter of drug prices note that for many drugs the patents granted as a way of encouraging research and investment create a monopoly situation within which the market cannot function effectively. In the face of a lethal disease, the only limit on what will be paid for a drug is the limit that prices impose on desperation-driven demand. The resultant price may, nevertheless, be very high indeed. In a careful reflection on the competing claims involved, Baruch Brody has concluded, “We need to develop a system of drug pricing that provides adequate economic incentives for drug research and development...while limiting excessive promotional costs and profits.”

Appeals to a sense of moral responsibility may have some impact on pricing policy by pharmaceutical firms, but inevitably it will take intervention on the part of governments to create a regulatory context that will limit the tendency to "excessive promotional costs and profits." What is crucial at this juncture is to recognize that the market price is not necessarily the fair price. Once that is recognized, it will be possible to engage in open and vigorous debate about how best to determine the fair price of drugs, crucial to the lives of sick people. One approach to the current untenable situation that places ARVs beyond the reach of those who might benefit from them would be for international organizations to undertake bulk buying agreements that would create a market context conducive to a significant lowering of prices.

International assistance

Even a radical reduction in the price of drugs will not resolve the problems confronted by the poorest of nations. Only significantly increased international assistance could begin to remedy this situation, however partially. While a right to health is enshrined in international covenants, vast inequities in the patterns of morbidity and mortality exist globally. Men, women, and children in the poorest nations routinely die of diseases that are treatable such as diarrhoea, acute respiratory infections and often still, TB.

Whether conceptualized as a moral duty or as an obligation to provide charitable assistance, the wealthy nations of the world can do far more to meet the burden of disease in the poorest nations. That they have failed to do so stands as a striking failure to respond to the desperate needs of the vulnerable. Typically, analysis of this problem from an ethical perspective focuses on the assurance of subsistence assistance that can guarantee the basic conditions for health and well being. Having failed to address these conditions, it is hard to imagine the kind of assistance that would be required to make access to very costly ARV therapies possible. A final dilemma that must be noted confronts donors who wish to provide ARV-related assistance. According to some conceptions of ethics, those who are the least advantaged have claims to priority when aid or assistance is considered. Yet in this instance it may be that assistance to nations that are more advantaged will make possible the provision of ARV treatment to a restricted number of citizens while the most impoverished nations would require much greater levels of assistance than are available to make any effective use of ARV treatment.

Access to antiretroviral treatment in resource-constrained nations

Given the cost of ARVs and the remote prospect that either international assistance or adjustments in drug pricing will fundamentally change the parameters that now prevail, many nations will need to approach the question of treatment for HIV infection with extremely limited capacity. In each nation, decisions about provision of ARVs will have to be made within broad sectoral determinations, e.g., the proportion of public resources that will be available for health care, education, social welfare, domestic security, national defense and other sectors. Even within the health sector, decisions will have to be made among competing claims, e.g., AIDS, malaria, maternal and child health. And within budgetary resources available for AIDS, choices will need to be made regarding allocations for prevention, the treatment of opportunistic infections, palliative care and ARVs. In the poorest settings, ARVs will be all but unavailable. A recent report from Uganda thus declared, "Antiretroviral drugs are not available in government health institutions nor in those run by religious organizations. Their availability is limited to private pharmacies or through direct ordering through various suppliers outside Uganda." On the other hand, in nations such as Brazil and Thailand, resources are sufficient to make possible government funded programmes guaranteeing access to at least some ARV treatments for certain groups. It is within these nations where resources permit some commitment of public funds to ARV treatment that it will be necessary to address the following questions:

- How does antiretroviral therapy link to broader health sector and community development objectives?

- Which, of the available alternatives, are realistically affordable given the country's resource constraints?
- Which of the affordable alternatives are most efficient in achieving a favourable development impact?

Empirical analysis will provide answers up to a point. But in the end these are fundamental policy and ethical choices. It will be crucial to recognize that there may be no right answers, and from an ethical perspective there may be some answers that are troubling and even violative of basic conceptions of fairness.

Levels of basic care

At its most fundamental level, the principle of justice requires that within a given society no individual be deprived of access to effective, socially affordable, medical treatment because of his or her inability to pay for such services, and that whatever patient costs are associated with care not represent an undue burden. Nations will differ as to how much they devote to health care as compared to other social needs. They will differ in terms of how much they devote to curative, as compared to preventive, interventions. Different countries will have different notions of the basic care to which each individual is entitled. Given available resources, no single standard can be applied to all countries. Nevertheless, some levels of general health provision may be so low, given the resources generally available, as to represent a violation of the obligation to assure a level of basic care to all.

The greatest good to the greatest number

In general, those interventions that will save the most lives or reduce suffering to the greatest extent have a stronger ethical claim than those that will benefit fewer individuals. There is, however, no easy way to measure and compare degrees of suffering. Nor are there simple ways to compare reduced suffering with extended longevity. Those responsible for allocating very scarce medical resources are thus engaged in a calculus of misery that requires an open, careful, and public weighing of the choices they must make. No single ethical principle exists that could resolve the current dilemmas.

Given these general considerations, it is clear that no policy that subjects AIDS care to invidious discrimination can be justified in ethical terms. Thus, for example, in societies wealthy enough to support dialysis for end-stage kidney disease, it would be ethically unjustifiable to deny access to ARVs, the cost of which is lower.

All or none?

Once a society has established an adequate, basic level of health care for its members, there remains the question of whether those with resources should be permitted to purchase that which is not otherwise provided. There are some conceptions of justice that claim that health care that is not available to all should not be available to any. According to this conception of justice, a multi-tiered health care system is, by its very definition, unjust. Others have asserted that such egalitarian requirements are incompatible with the willingness to tolerate differentials in wealth and income.

Let those who can pay, obtain treatment?

The issues posed by these competing conceptions of justice have special relevance to the dilemma posed by ARVs in poor nations where such therapy is not generally affordable. Should those who can afford such therapy for HIV disease be permitted to purchase the needed drugs for their own use? Should physicians trained, at least in part at the public's expense, be permitted to dispense such drugs? Should governments supervise the provision of care to assure that it meets currently accepted international and scientific standards? Those who claim that individuals should be permitted to gain access to treatments not otherwise available warn of black markets in the face of restrictions. They argue that it would be cruel to deny individuals the right to use their own resources to extend their lives and the lives of family members. There are remarkably few voices arguing the case for an egalitarianism that would require all to share a common trajectory of HIV fatality.

Rationing under circumstances of scarcity

When, because of severe economic constraints, it is impossible to provide ARVs in the combinations now considered the standard of care in economically advanced nations to all individuals who might clinically benefit, it might, nevertheless, be both cost beneficial and ethically defensible to provide access to selected classes at public expense. This is the classic circumstance of rationing: when all cannot be served, is it justifiable to aid the few? If such aid is justified, on what morally defensible ground does the selection process occur?

Special cases

A case can be made for the identification of numerically restricted classes of individuals who could benefit from the time-limited prophylactic use of ARVs. Three groups will be discussed in this regard: health care workers exposed to the infected blood of their patients, the victims of rape, and pregnant women.

Health workers

Should health workers, who have been exposed to the infected blood of their patients, be offered ARV treatment to reduce the likelihood that they will become infected? Would the provision of such treatment to health care workers, when their patients do not have access to ARVs, be unfair?

The risk of transmission of HIV-infection by accidental needle stick wounds is approximately 0.3%. A recent study has suggested that the immediate initiation of treatment with ARVs may reduce that risk by upwards of 75%. Such treatment is normally prescribed for one month. The case for the provision of such prophylactic intervention takes the following form: first, health care workers are needed to care for hospitalized patients with HIV disease. If, in the course of their work, they are exposed to HIV and, as a consequence, become infected, develop disease, and are lost to the pool of workers capable of caring for patients with HIV infection, then society in general, and patients with HIV in particular, would lose out. Thus, patients who themselves do not have access to ARVs have an interest in prophylactic provision to health care

workers. Second, if the failure to provide post-exposure prophylaxis would reduce the willingness of health care workers to care for patients with HIV, then both society and patients with HIV would have an interest in permitting this limited intervention. Third, society has a special responsibility to those who assume even limited risks associated with caring for those with HIV infection. A final claim on behalf of post-exposure prophylaxis is that since the number of eligible individuals would be relatively small, the cost incurred by such an effort could be affordable in at least some resource-constrained countries. This position has been challenged by some economists who have asserted that post-exposure prophylaxis is not cost-effective in any setting, even the wealthiest. In the end, a decision must be made about whether the unique moral claims posed by exposed health care workers warrant an intervention that cannot be justified on narrowly economic grounds.

There is a further ethical complication in the special claims of exposed health workers. The arguments could logically be extended to assert that when prophylaxis fails, treatment with ARVs should be continued. Once ARV therapy with a potential for life-extending benefits is begun, can it rightfully be interrupted? Would not such an interruption represent a kind of cruelty? Hence a case would have been made for a special class of individuals in terms of ongoing treatment. The strength of the argument for access to ARVs in post-exposure circumstances lies in limiting the intervention to the purposes of prophylaxis. Failure to do so would create a privileged class with access to treatment based on how they became infected, and that would raise profound questions of fairness.

Victims of rape

Based on studies involving health care workers accidentally exposed to HIV infected blood from their patients, it is assumed that victims of rape may also benefit from ARV prophylaxis designed to reduce the risk of HIV infection. Victims of rape have a special claim based on the profound assault to which they have been subjected. To the extent that a society can afford to provide treatment that could, at a minimum, reduce the risk of infection with HIV, it ought to respond to that unique circumstance. But, unlike the case of exposed health care workers, where it is almost always possible to determine the source-patient's HIV status - and thus weigh the cost/benefit of initiating intervention - it may not be possible to determine the HIV status of the rapist, who may not be apprehended in time or may never be identified. This would be possible with PCR and serology on semen but these tests are very unlikely to be available for cases of rape in developing countries. Therefore, the offer of post-rape prophylaxis would unfortunately concern a large number of women and would entail a significant cost in very resource-constrained societies. In societies where resources are not so limited, the moral claims of rape victims are strong indeed.

The discussion of those who have been raped quite naturally leads to the question of whether ARV prophylaxis ought to be available to those who believe they may have been exposed to HIV in consensual sex, either because of condom breakage or because of a failure to employ condoms during sexual intercourse. Those who claim that no distinction ought to be made between such individuals and rape victims wish to avoid the implication that the former are "guilty" while the latter are innocent. Proponents of treating rape victims present two arguments: First, the special claim of rape victims stems from the trauma to which they have

been subjected. It may be argued that those placed at risk by consensual sex must assume responsibility for such risk (such as condom breakage) which any consenting adult assumes today in his or her sexual relations. Secondly, there is a fear that treating ARV prophylaxis as a "morning after" intervention may subvert prevention messages that stress the importance of practicing safer sex and the avoidance of unprotected sexual intercourse with those whose HIV status is unknown.

Pregnant women

In 1994, a clinical trial (ACTG 076) in the United States and France demonstrated that the provision of ZDV monotherapy during pregnancy (oral therapy during pregnancy, intravenous ZDV during labour and oral therapy for the newborn for six weeks after birth) could reduce by 66 percent the risk of vertical transmission of HIV. This finding represented the first indication that ZDV could serve so critical a preventive function. Soon after those results were made public, treatment with ZDV became the standard of care for infected pregnant women in the United States. In 1988 it was demonstrated that a one month course of oral ZDV during the last month of pregnancy could also reduce the risk by around 50%. The importance of combination therapy with ARVs (including a protease inhibitor) for all infected women, whether or not they are pregnant, for the treatment of HIV infection, was convincingly demonstrated in 1995.

In settings where ARV therapy is not available for all infected women, the question arises whether it would be ethical to offer ZDV to pregnant women for the sole purpose of reducing the risk of vertical transmission? Some nations, too poor to afford ARV treatment for all who could benefit, might be able to afford the much more limited expenditure of resources that would be entailed in the preventive use of ZDV during pregnancy - although there is controversy on this matter.

Some believe that offering treatment to women only during pregnancy and solely for the purpose of reducing the risk of vertical transmission would represent an immoral transformation of women into mere "vessels of reproduction." Further, they argue that to stop treatment once it had started would be cruel. Advocates of the special treatment of pregnant women argue, on the other hand, that such efforts offer a woman the unique opportunity to save the life of her child; that the interruption of treatment after delivery would simply return her to the status of her compatriots who share the burden of living in conditions that do not permit ARV treatment. Finally, advocates stress that the offer of special treatment during pregnancy entails no obligation to accept treatment in the interest of the child. They note that while some women might refuse to accept such treatment, many would not. Thus, they assert, respect for women is best demonstrated by offering such intervention where affordable rather than withholding it because of concerns about the interests of women as a vulnerable class.

By way of summary, where resources do not permit universal treatment with ARVs, it is ethically permissible to provide such care to some special sub-groups whose claim to intervention may set them apart from the general population. The cases described above entail interventions of limited duration, designed to serve the function of prophylaxis. No strong ethical arguments can be made to give special priority for *treatment* to groups for whom *prophylactic intervention* might provide a clear benefit. Under such circumstances, open and

candid discussion of why decisions have been made will provide the surest guarantee against arbitrariness and invidious discrimination.

ZDV monotherapy for treatment of HIV infection

In economically advanced nations, antiretroviral monotherapy is now regarded as substandard because of the pattern of HIV resistance that develops thus limiting the effectiveness of therapy for the patient and raising the spectre of resistance to antiretroviral therapy on a population-wide scale. Can therapy, which is suboptimal in economically advanced nations, be acceptable in resource-constrained nations? The answer to this question requires a careful clinical assessment of the benefit for the individual of monotherapy and of the epidemiological risks entailed. To the extent that monotherapy offers the prospect of some, albeit limited, benefit to a patient, such therapy should be offered after a full, culturally appropriate explanation of the risks and benefits of such treatment. It would be difficult to justify, either clinically or ethically, depriving patients of the limited benefits of monotherapy because of the far greater benefits of multi-drug ARV therapy, which is utterly inaccessible. The risks of community resistance are present under such circumstances and should be weighed against the benefits to patients of monotherapy and the limited prospect that other therapies will become available which will be ineffective because of resistance.

Paternalism, public health, and the problem of resistance

Where resource constraints do not provide a barrier to care, it may be necessary to consider the question of whether some patients should be denied ARVs for clinical and public health reasons.

For decades, the problem of securing adherence to extended treatment regimens for chronic conditions has been the subject of clinical concern as studies have consistently demonstrated low rates of adherence. Given such difficulties, the challenges involved in combination ARV therapy for HIV disease are daunting. Full regimens may require up to 15-20 pills daily. Some of these drugs must be taken on an empty stomach, others following a meal. Side effects, which may include nausea, diarrhoea, vomiting and anorexia, may make adherence even more difficult.

Non-adherence and the development of resistance

Inadequate adherence has profound implications. A rapid rate of viral replication, combined with a high rate of mutation, can lead to the development of resistance particularly in the presence of selective pressure by antiretroviral therapies. Resistance can develop if drug doses are inadequate or doses are missed. In early trials of protease inhibitors, patients received sub-optimal dosages, and HIV readily developed resistance which persisted even when higher doses were administered. Another unfortunate result can be cross resistance to alternative HIV treatments not yet tried.

The individual's right to treatment and the public health interest

The prospect of resistance not only makes individual patients vulnerable to strains of HIV that are unresponsive to treatment but raises the spectre of a public health threat that could neutralize recent therapeutic advances.

The threat of the emergence of drug resistance as a result of non-adherence raises profound ethical questions. Should some therapies not be offered to patients who might have difficulty in adhering to the demanding regimens? Should such concerns ever be cause for denying drug therapies to patients who request them? Should decisions to withhold combination therapies be based on demonstrated non-adherence with previous treatment demands or on predictions about future behaviour based on defined patient characteristics? Are there entire classes of individuals, eg., the homeless, those suffering from certain types of mental illness, or injecting drug users, to whom the drugs ought not be offered?

Overriding patients' wishes for their own good?

Can predictions about patient adherence ever provide a justification for denying individuals treatment because of concerns about how the prospect of resistance would affect their own well being? From some ethical perspectives, the principle of autonomy must always guide clinical decision making. A patient fully informed of the risks of non-adherence must, from this perspective, be given the opportunity to take those risks in light of the potential benefits of therapy. Alternatively, those who believe that physicians have an ethical obligation to protect their patients' well being, even when that entails overriding patient preferences, assert that denial of access to ARVs can be justified on grounds of paternalism. Those who adhere to the paternalistic position argue that it would represent an abrogation of professional responsibility to prescribe ARVs under such circumstances.

Protecting third parties

The issue is clearly not one of individual patient welfare alone. Failure to adhere to therapy may have profound public health consequences, most notably the development of resistant strains of HIV which could be transmitted to sexual and needle sharing partners as well as to the infants born to infected women. From this perspective, the issue is not a matter of limiting autonomy in order to protect the patient from the consequences of non-adherence, but is rather the protection of third parties from potential harm.

ARVs present a unique conflict

Even those who are committed to the protection of patient autonomy recognize that autonomy is not an absolute and may be overridden when the wellbeing of the community is at stake. Typically, this occurs in the context of infectious diseases, such as tuberculosis, where patients may be compelled to undergo testing and treatment. The interests of the public health and the patient are served by such mandatory measures. What makes the ARV situation so unique and so potentially troubling is that the public health interest may, in some circumscribed circumstances, be placed in conflict with the preference of the patient *for* therapy.

Poverty and homelessness as factors in non-adherence

Denial of access to therapy, whether on public health or paternalistic grounds, should never be based upon broad social characteristics such as mental illness, homelessness or drug use, but should only follow a careful individualized assessment of the likelihood of non-adherence. It is especially crucial to guard against the influence of preconceptions that may bias clinical decision makers against entire classes of patients. When patients are denied access to treatment, they must be apprised of the rationale for withholding therapy, and such decisions must be reviewed periodically, as changed patient behaviour could affect further clinical decisions. To the extent that social circumstances such as homelessness or inadequate access to mental health services or drug abuse treatment, create the context which threatens adherence, justice demands that those underlying conditions be addressed. It would be a cruel irony to deny the most vulnerable and marginalized access to potentially life-extending therapies when remediable social conditions contribute to their inability to adhere to therapies.

Directly Observed Therapy: a useful approach with ARVs?

The problem of resistance induced by non-adherence has been at the centre of discussions regarding tuberculosis for more than four decades. With the increase in tuberculosis in the late 1980s--driven in part by the HIV epidemic--and the prevalence of multi-drug resistant tuberculosis, directly observed therapy (DOT) emerged as the standard of care internationally. Under DOT, patients are required to take their medication in the presence of a health care worker or person charged with the responsibility of assuring that individuals in fact take their prescribed medication. Viewed as an intrusion by some, as a service by others, DOT was thought to be the only way to ensure that patients continued to take their medication for the many months during which they no longer felt sick but were not yet cured. The sheer logistics of combination therapies involving ARVs, which require, at this juncture, medications several times a day over very extended periods, perhaps life-long, preclude DOT as a useful approach. Programme planners must, however, draw lessons from the experience of DOT in the creation of clinical and social support networks that enhance the prospects of treatment adherence.

Physicians' responsibilities in maximizing adherence

Finally, the threat of viral resistance must also be understood in the context of physician practices. Failure to provide appropriate combinations of ARVs at appropriate dosage levels could produce resistance even in patients who are completely adherent. Thus, there is a strong professional obligation among physicians to understand how these drugs should be prescribed. Physicians must be supported in their efforts by institutional mechanisms that provide appropriate, ongoing education and the necessary tests that will permit the careful monitoring of patients undergoing ARV treatment. For example, careful monitoring of the clinical course of women being provided with ZDV monotherapy for the prevention of vertical transmission would limit the extent to which such medication might be diverted to other patients for the inappropriate treatment of HIV infection with ZDV monotherapy.

To the extent that resources permit, public health authorities should monitor the prevalence and patterns of drug resistant HIV so that the impact of physician practices and patient behaviours may be tracked. Furthermore, in the face of severely constrained resources, knowledge about patterns of resistance could shape the most appropriate use of health care funds.

Ethics in antiretroviral research

Benefits for the subjects used in clinical trials

Since so much of the contemporary approach to HIV infection is based on therapeutic agents and regimens that place treatment beyond the reach of all but the wealthiest of nations, one approach to remedying the situation is to undertake research to develop less costly therapies. From this perspective, it becomes clear that the longstanding ethical principle that research in poor countries must ordinarily involve therapies that will be affordable, if proved effective, must remain fundamental. No level of risk in research that will produce findings that cannot benefit the subject population is ethical.

Stopping treatment at the end of the trial and the danger of viral rebound

While there is broad consensus on such general principles, controversy arises in particular cases where competing ethical norms provide no easy guide to decision makers. How, for example, is one to consider the ethics of research that provides to one group of subjects the current standard of double or triple combination ARV therapy when it is clear that at the end of the study such therapy will be withdrawn from the study population? On a clinical level, it is understood that the termination of therapy will almost certainly result in an abrupt rise in viral load and a rebound in disease. Does this violate the principle established by the Council for International Organizations of Medical Services that research should never leave subjects worse off than before the study trial commenced? Does a fully informed, culturally appropriate consent, which explains the risk entailed, make it ethically acceptable? Does the additional risk, beyond that which would have prevailed in the absence of the clinical trial, fall within acceptable bounds given the potential benefits of the research? Is there an obligation for sponsoring agencies to provide those who received the multi-drug ARV arm of a clinical trial with continued treatment even when such care is not generally available to the population from which the research subjects were drawn? Clearly these issues require the attention of ethical review panels in both sponsoring and host nations.

Placebo-controlled trials of ZDV in pregnant women in poor nations

It is widely acknowledged that the regimen used in clinical trial 076 is unaffordable for most women with HIV infection. Therefore, trials of modified approaches to preventing the vertical transmission of HIV have been conducted. Research on vertical transmission of HIV took place under morally troubling conditions: the gross inequalities in global access to ARVs. The dispute centred on the question of whether a placebo-controlled trial is ethical given that 076 provided a standard of care in wealthy nations. Fortunately, in April 1998, this dilemma was resolved. After a trial in Thailand found a short course of ZDV to be effective in reducing mother to child transmission of HIV infection, all placebo arms of ongoing trials were stopped.

Conclusions

It is a striking feature of the global AIDS pandemic that the new combination therapies and the antiretrovirals upon which they are based are virtually unavailable where the disease poses the

greatest threat. This situation is, of course, not dissimilar to the more general pattern that prevails in medicine, but it is unique in that it is within recent memory that the advanced industrial world shared with the most impoverished nations a common fate of relative therapeutic impotence in the face of HIV infection.

Given the current cost of the new drug therapies, there is little likelihood that they will become widely available where they are so desperately needed. And, indeed, given the relative importance of prevention in nations where the incidence of infection is still alarmingly high, it is unclear, even were ARVs marginally more affordable, that investment in such therapeutic agents would be a wise use of resources. This state of affairs is a consequence of deep and widening gulfs in wealth between and within countries, a profound inequality that should fuel our moral concern. It also underscores the importance, despite recent advances in therapeutics, of a continued commitment to the development of vaccines that are inexpensive and easy to administer. Only such a vaccine will meet the needs and moral claims of the poorest nations for effective AIDS prevention. Those claims will be harder to press if, because of antiretroviral therapies, HIV disease becomes a more manageable and less threatening disease in the richest nations of the world. Many tens of millions of individuals will still be at risk of an infection which for them remains lethal. For this reason, continued and reinforced effort to prevent HIV infection remains an ethical and public health imperative.

Further Reading

1. Bangsberg D, Tulsky JP, Hecht FM, et al. Protease inhibitors in the homeless. *Journal of the American Medical Association* 1997; 278:63-65.

2. Bayer R and Stryker J. Ethical challenges posed by clinical progress in AIDS. *American Journal of Public Health,* 1997, October.

3. Brody B. Public goods and fair prices: Balancing technological innovation with social well being. *Hastings Centre Report* 1996; 26:5-11.

4. Deeks SG, Smith M, Holodnly M, et al. HIV-1 protease inhibitors: A review for clinicians. *Journal of the American Medical Association* 1997; 277:145-153.

5. Levine RJ. "International Codes and Guidelines for Research Ethics: A Critical Appraisal" in Vanderpool, Hy (ed) The Ethics of Research Involving Human Subjects: Facing the 21st Century. (Frederich, Maryland: University Publishing Group, Inc., 1996).

6. Shue H. Basic Rights: Subsistence, Affluence and U.S. Foreign Policy, 2nd ed. (Princeton, New Jersey: Princeton University Press, 1996).

7. Floyd K and Gilks G. Cost and financing aspects of providing antiretroviral therapy in *The implications of antiretroviral therapy*, Van Praag E, Fernyak, S and Martin Katz A. World Health Organization, Geneva, 1997.

8. Van Praag E, Perriens JH. Caring for patients with HIV and AIDS in middle-income countries. *British Medical Journal*, 1996; 313: 440

Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA, donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as an immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia
CH-1211 Geneva 27

Tel: 41 22 791 4651
Fax: 41 22 791 4187

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